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Emerging therapies for Parkinson's disease: From bench to bedside

F.I. Tarazi [a,*], Z. Sahli [a,c], M. Wolny [b], S.A. Mousa [b]

[a] Department of Psychiatry and Neuroscience Program, Harvard Medical School, McLean Hospital, Belmont, MA 02478, USA
[b] The Pharmaceutical Research Institute at Albany College of Pharmacy and Health Sciences, Rensselaer, NY 12144, USA
[c] School of Medicine, American University of Beirut, Beirut, Lebanon

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ABSTRACT

The prevalence of Parkinson's disease (PD) increases with age and is projected to increase in parallel to the rising average age of the population. The disease can have significant health-related, social, and financial implications not only for the patient and the caregiver, but for the health care system as well. While the neuropathology of this neurodegenerative disorder is fairly well understood, its etiology remains a mystery, making it difficult to target therapy. The currently available drugs for treatment provide only symptomatic relief and do not control or prevent disease progression, and as a result patient compliance and satisfaction are low. Several emerging pharmacotherapies for PD are in different stages of clinical development. These therapies include adenosine A_{2A} receptor antagonists, glutamate receptor antagonists, monoamine oxidase inhibitors, anti-apoptotic agents, and antioxidants such as coenzyme Q10, *N*-acetyl cysteine, and edaravone. Other emerging non-pharmacotherapies include viral vector gene therapy, microRNAs, transglutaminases, RTP801, stem cells and glial derived neurotrophic factor (GDNF). In addition, surgical procedures including deep brain stimulation, pallidotomy, thalamotomy and gamma knife surgery have emerged as alternative interventions for advanced PD patients who have completely utilized standard treatments and still suffer from persistent motor fluctuations. While several of these therapies hold much promise in delaying the onset of the disease and slowing its progression, more pharmacotherapies and surgical interventions need to be investigated in different stages of PD. It is hoped that these emerging therapies and surgical procedures will strengthen our clinical armamentarium for improved treatment of PD.

Contents

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder that currently affects over 1 million Americans with about 40,000–50,000 new cases diagnosed every year. The prevalence of PD increases with age, with the normal age of onset being around 65 years old. It is estimated that the number of Parkinson's disease patients will increase from 4.1 million in 2005 to 8.7 million in 2030. The lifetime risk for PD in men is 2.0%, while in women it is 1.3%. There are also cases known as early-onset PD where the disease manifests in individuals around the age of 45, but these only comprise a small portion of the PD population (Tanner et al., 1997; McNaught & Olanow, 2006; Rao et al., 2006).

PD typically presents in a sporadic idiopathic fashion (Cookson & Bandmann, 2010). Hereditary factors play a minimal role because only 10% of all PD cases are found to have genetic links involved, and these

* Corresponding author at: Harvard Medical School and McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA. Tel.: 617 855 3176; fax: 617 855 3479.
E-mail address: ftarazi@hms.harvard.edu (F.I. Tarazi).

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are most closely associated with early-onset PD (Bekris et al., 2010). For example, autosomal recessive inheritance linked to the *PARKIN* gene has been reported in a large number of early-onset cases (Polymeropoulos et al., 1997; Kitada et al., 1998). Other suspected causes include environmental toxins, medications, and viruses that all result in an increase in oxidative stress (Di Monte et al., 2002; Jenner & Olanow, 2006). Oxidative stress leads to generation of free radicals, which induces apoptotic cell death in dopamine neurons, particularly those neurons projecting from the substantia nigra *pars* compacta to the caudate-putamen (Baldessarini & Tarazi, 1996; Naoi & Maruyama, 1999). Some of the dopaminergic neurons that survive contain Lewy bodies, which consist of aggregates of proteins thought to cause neurodegeneration (McNaught, 2004; Olanow & McNaught, 2006). However, it remains to be determined if the Lewy bodies cause the neurodegeneration of dopamine neurons or result from such a process.

1.1. Clinical symptoms and diagnosis

PD symptoms vary among patients and may include tremor [e.g. hand tremor at rest], loss of spontaneous movements, facial expression and eye blinking [akinesia and bradykinesia], muscle rigidity, impaired posture and balance, and changes in speech fluency [reduced volume and clarity] and handwriting [less legible] (Tolosa et al., 2006; Jankovic, 2008; Pahwa & Lyons, 2010). Patients are typically diagnosed based on their medical history and an extensive neurological and physical examination. The diagnosis is likely when two out of the four cardinal symptoms of PD [tremor, rigidity, akinesia, and postural instability] are present (Hermanowicz, 2001). Brain scans are used to rule out related disorders like progressive supranuclear palsy, drug-induced parkinsonism, vascular parkinsonism, and diffuse Lewy body disease (Piccini & Whone, 2004; Piccini & Brooks, 2006). Non-motor symptoms including memory impairment, executive deficits, sleep disturbances, depression, hallucinations as well as autonomic nervous system dysfunction resulting in constipation, urinary frequency and incontinence, and orthostatic hypotension are also common, and can significantly impair the daily activities and well being of PD patients (Chaudhuri et al., 2006; Lyons & Pahwa, 2011).

Q3 [^{123}I]ioflupane [N-u-fluoropropyl-2a-carbomethoxy-3a-(4-iodophenyl) nortropane, and known commercially as DaTSCAN] was approved in 2011 as a tool for the accurate diagnosis of PD (Bajaj et al., 2013). DaTSCAN is a radiotracer that binds to striatal dopamine transporters to be used in neuroimaging with a single photon emission computed tomography (SPECT) (Benamer et al., 2000). Nonetheless, the accuracy and sensitivity of DaTSCAN in the diagnosis of PD were identical to clinical diagnosis, raising doubts about the advantages of using this tool to confirm the diagnosis of PD (de la Fuente-Fernandez, 2012). Postmortem neuropathological examination of brain tissue from PD patients remains the superior choice to accurately confirm the diagnosis of PD (Michotte, 2003).

1.2. Current pharmacotherapies

Dopamine is a catecholamine neurotransmitter found predominately in the central nervous system. The first step in dopamine synthesis is the hydroxylation of the essential amino acid tyrosine to L-dihydroxyphenylalanine (L-DOPA) by the rate-limiting enzyme tyrosine hydroxylase with molecular oxygen, tetrahydrobiopterin and iron as cofactors. The second reaction is the conversion of L-DOPA to dopamine by the enzyme aromatic L-amino acid decarboxylase (DOPA decarboxylase) with pyridoxal phosphate (PLP) as the cofactor (Elsworth & Roth, 1997; Kandel et al., 2000). Dopamine is inactivated by three enzymes: monoamine oxidase (MAO), aldehyde dehydrogenase (ALDH) and catechol-O-methyl transferase (COMT), to produce inactive metabolites including 3,4-dihydroxyphenyl-acetaldehyde (DOPAC), homovanillic acid (HVA) and 3-methoxytyramine (3-MT). In the striatum, dopamine is inactivated by reuptake via the dopamine transporter, then enzymatic breakdown by MAO into DOPAC. In the prefrontal cortex, where dopamine innervations are lower than in striatum, dopamine is inactivated by reuptake via the norepinephrine transporter and enzymatic breakdown by COMT into 3-MT (Elsworth & Roth, 1997; Kandel et al., 2000).

Pharmacotherapies that are currently used for treatment of PD focus only on the symptomatic component of the disease by attempting to replenish the dopamine content in the brain, but these therapies do not prevent the progression of the disease. L-DOPA remains as the gold standard because it can readily cross the blood brain barrier (BBB) and is converted to dopamine by the actions of the enzyme DOPA decarboxylase (Hornykiewicz, 2002). Because L-DOPA is also converted into dopamine in the peripheral nervous system, causing undesirable adverse events such as nausea and vomiting, it is standard in clinical practice to co-administer L-DOPA with DOPA decarboxylase inhibitor such as carbidopa that does not cross the blood–brain barrier. This inhibition can reduce conversion of L-DOPA to dopamine in the peripheral tissue and therefore increase L-DOPA delivery to the brain (Nagatsua & Sawadab, 2009). A controlled release formulation of levodopa/carbidopa [Sinemet CR®] is also available to provide more sustained levodopa plasma levels than standard levodopa/carbidopa [Sinemet®] (Rodnitzky, 1992). Nonetheless, long-term levodopa treatment is associated with significant complications including involuntary movements, dyskinesias, and response fluctuations "wearing off" effect (Jankovic, 2005). Another levodopa formulation that combines levodopa/carbidopa with the COMT inhibitor entacapone in a single tablet [Stalevo®] is also available for treatment of PD patients (Silver, 2004). COMT inhibitors are not effective independently, but they prolong the availability of levodopa to the brain and are clinically beneficial as adjunctive treatment to levodopa therapy in PD patients with end-of-dose fluctuations (Ruottinen & Rinne, 1998). Other valid pharmacotherapies include dopamine agonists, which typically target dopamine postsynaptic D_2 receptors. Among these agents are the ergot derivatives bromocriptine [Parlodel®], lisuride [Dopergin®], pergolide [Permax®], and cabergoline [Dostinex®], as well as other agents that do not possess the ergot structure, such as pramipexole [Mirapex®] and ropinirole [Requip®] (Tintner & Jankovic, 2003).

Nonetheless, all approved PD pharmacotherapies have limited efficacy, do not prevent the progression of the disease, and are associated with adverse motor and non-motor side effects. Accordingly, there is an urgent need to develop novel therapies that are superior to the current therapies. This review will discuss the main emerging pharmacological therapies and non-pharmacological interventions that are in development for improved treatment of PD.

2. Emerging pharmacotherapies

Since current treatments do not provide adequate neuroprotection and are incapable of slowing the progression of PD, there is a great need to develop novel pharmacotherapies with improved efficacy, safety, and long-term maintenance. The following are various agents that are currently in different stages of preclinical and clinical development.

2.1. Adenosine A_{2A} receptor antagonists

The pathology of PD involves different nuclei in the basal ganglia, the brain region responsible for programming and execution of movement (Albin et al., 1989). Due to nigrostriatal dopamine loss, the basal ganglia output is less active than in a normal human brain (Penney & Young, 1986). The adenosine A_{2A} receptors are abundant in striatum and other nuclei of the basal ganglia, as well as in nucleus accumbens and olfactory bulb, where they are co-localized selectively with the DA D_2 receptors (Rosin et al., 2003). An antagonistic functional interaction appears to exist between D_2 and A_{2A} receptors in the basal ganglia (Feigin, 2003). Experimental data suggest that the improvement of mobility in

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PD patients could be achieved with the activation of D_2 receptors and inhibition of adenosine A_{2A} receptors (Cieślak et al., 2008).

Istradefylline, which is an analog of caffeine and an adenosine A_{2A} receptor antagonist, has been shown to be safe and effective when added to levodopa therapy. Istradefylline is approved for adjunctive treatment of PD in Japan but has not been approved and is no longer in clinical development for PD treatment in the USA (Dungo & Deeks, 2013). Two clinical studies demonstrated efficacy and safety in small PD patient populations. Levodopa "off" time, characterized by the return of parkinsonian symptoms towards the end of a dosing period, and levodopa-induced dyskinesias were both significantly reduced after adjunctive treatment with istradefylline (Bara-Jimenez et al., 2003; Hauser et al., 2003). Another adenosine A_{2A} receptor antagonist, preladenant, also demonstrated promising results in phase II trial by providing sustained "off" time reductions and "on" time increases (Hauser et al., 2011) and displaying favorable safety profile (Cutler et al., 2012). Nonetheless, this compound failed to demonstrate adequate efficacy in phase III trials whether as a monotherapy or adjunctive therapy to levodopa, and its clinical development was terminated (Merck Press Release, 2013). Development of a third A_{2A} antagonist was also discontinued due to preclinical findings (Vernalis Press Release, 2010). In spite of these failures, several A_{2A} compounds such as tozadenant, PBF-509, ST1535, ST4206 and V81444 remain in different stages of preclinical and clinical development (Pinna, in press).

2.2. Glutamate receptor antagonists

Glutamate (Glu), a major excitatory neurotransmitter in the brain, exerts its neural effects by interacting with two major groups of Glu receptors, the ionotropic (coupled to ion channels) and metabotropic (coupled to intracellular second messengers) types (Ozawa et al., 1998; Récasens et al., 2007). There are three subtypes of ionotropic Glu receptors: *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate (KA; Ozawa et al., 1998). Glutamate has been implicated in the pathophysiology of PD as well as in levodopa-induced dyskinesias, suggesting that blockade of specific glutamate receptor subtypes would enhance levodopa therapy (Chase et al., 1998; Merims et al., 2001; Calon et al., 2003). However, compounds that inhibit NMDA receptors such as amantadine have proven mildly effective in PD, particularly against dyskinesias and motor fluctuations (Papa & Chase, 1996; Blanchet et al., 1998; Verhagen et al., 1998), though these findings remain unconfirmed (Thomas et al., 2004; Jahangirvand & Rajput, 2013).

Talampanel (LY-300164) is a non-competitive AMPA receptor antagonist (Bleakman et al., 1996; Lodge et al., 1996). Talampanel was administered to MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine)-lesioned monkeys exhibiting Parkinson-like symptoms and treated with or without levodopa (Konitsiotis et al., 2000). When used as monotherapy, the drug was ineffective in reducing PD symptoms. However, when co-administered with levodopa, talampanel significantly increased motor activity by 86% and reduced levodopa-induced dyskinesias (LID) by 40% (Konitsiotis et al., 2000). Talampanel requires further evaluation in clinical trials in PD patients to validate its efficacy and tolerability. In contrast, clinical trials utilizing perampanel, another AMPA receptor antagonist, failed to show improvement in PD symptoms or reduction in dyskinesia in drug- vs. placebo-treated patients (Eggert et al., 2010; Lees et al., 2012).

Clinical trials with the metabotropic mGluR5 receptor antagonist AFQ056 found that this drug was able to alleviate motor symptoms in patients with moderate to severe LID and on stable dopamine therapy compared to placebo-treated patients (Berg et al., 2011). Another trial also demonstrated significant antidyskinetic effect without worsening of motor symptoms with AFQ056 (Stocchi et al., 2013). Both trials, however, were associated with undesirable adverse events including fatigue, psychiatric and gastrointestinal disorders (Berg et al., 2011; Stocchi et al., 2013). A third randomized, double-blind, placebo-controlled clinical trial with dipraglurant (AX48621), a negative allosteric modulator of mGluR5, reported improvement in LID with favorable safety profile (Tison et al., 2013). Additional trials with antagonists or allosteric modulators of glutamate receptors are needed to assess the long-term efficacy, safety and tolerability of these compounds in PD patients.

2.3. Monoamine oxidase inhibitors

Monoamine oxidase B (MAO-B) inhibitors can increase synaptic dopamine by blocking its degradation. Two MAO-B inhibitors, selegiline [Eldepryl®] and rasagiline [Azilect®], are currently approved for the symptomatic treatment of early Parkinson's disease and to reduce off-time in patients with more advanced Parkinson's disease and motor fluctuations related to levodopa (Schapira, 2011). These agents, however, have limited use in clinical management of PD due to suboptimal therapeutic efficacy and possible drug interactions with medications that are contraindicated when taken with MAO inhibitors (Chen, 2011). A third MAO-B inhibitor, safinamide, is being developed as a once daily add-on therapy for PD patients taking L-DOPA or dopamine agonists to improve motor function without worsening dyskinesia (Fariello, 2007; Schapira, 2010; Grégoire et al., 2013; Schapira et al., 2013). Safinamide administration of 50 mg/day and 100 mg/day significantly decreased "off" time and increased "on" time in PD patients compared to the placebo-treated PD patients. Furthermore, safinamide 100 mg/day improved activities of daily living scores, emotional well-being, communication, and bodily discomfort versus placebo (Borgohain et al., 2014). Clinical studies found that safinamide exhibits Q4 a relatively benign safety profile with no clinically meaningful differences between PD patients receiving safinamide and placebo-treated PD patients for measurements of vital signs, electrocardiogram variables, or physical, neurological, or ophthalmologic examinations (Schapira et al., 2013; Borgohain et al., 2014). Nevertheless, additional Q5 trials are still needed to determine the optimal clinical efficacy of safinamide in PD patients.

2.4. Anti-apoptotic agents

Programmed neuronal cell death in PD appears to occur by apoptosis rather than necrosis (Tatton et al., 1998; Hirsch et al., 1999; Hartmann et al., 2000). The c-Jun-N-terminal kinase (JNK) pathway influences neuronal apoptosis by activating the transcription factor c-Jun at serine residues (Kyriakis et al., 1994). The JNK signaling cascade is in turn regulated by the small GTPases rac and cdc42 (Teramoto et al., 1996). Activation of cdc42 or of kinases down-stream of cdc42 and upstream of JNK can trigger neuronal apoptosis, and therefore this pathway may represent a potential target for novel PD pharmacotherapies by blocking early signals that may lead to commitment to neuronal death (Maroney et al., 1999).

CEP-1347, an anti-apoptotic agent and a selective inhibitor of the mixed-lineage kinase (MLK) family (Maroney et al., 2001; Murakata et al., 2002), was shown to be effective in vitro at halting apoptosis (Saporito et al., 1999, 2000). A small clinical trial enrolling 30 PD patients reported that CEP-1347 was safe and well tolerated with no acute effects on parkinsonian symptoms or levodopa pharmacokinetics (Parkinson Study Group, 2004). These findings encouraged testing CEP-1347 in a larger randomized, double-blind, placebo-controlled clinical trial (PRECEPT), which enrolled 806 patients with early PD not yet requiring dopaminergic therapy. The study was terminated early after planned interim analysis showed no evidence or pattern of improvement in patients receiving one of three tested doses of CEP-1347 (10 mg BID, 25 mg BID, or 50 mg BID) vs. placebo, and it was concluded that despite the potential promising findings of CEP-1347 in preclinical models, the compound failed to be an effective treatment in early PD (Parkinson Study Group PRECEPT Investigators, 2007). Novel and more effective anti-apoptotic agents that can selectively block the death of neuronal cells of interest with a benign safety profile remain

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interesting candidates for delaying the progression of neurodegenerative diseases including PD (Sureda et al., 2011).

2.5. Antioxidants

Oxidative stress and generation of free radicals and reactive species in neurons and glial cells have been hypothesized to trigger neurodegeneration in PD (Hauser & Hastings, 2013). Oxidative damage to lipids, proteins and DNA can impair cell viability in PD patients (Jenner, 2003). The occurrence of oxidative stress in PD patients is supported by postmortem studies and by preclinical studies showing the ability of oxidizing toxins to induce cell death in the substantia nigra (Olanow et al., 1998). Accordingly, antioxidants that scavenge free radicals and reactive species may have beneficial therapeutic effects in PD by preventing the onset of apoptotic cell death and neuronal degeneration of the dopaminergic nigrostriatal pathway (Jenner, 2003). The following are the most commonly investigated antioxidants:

2.6. Coenzyme Q10

Exposure to the neurotoxin MPTP in animal models inhibits the mitochondrial electron transport chain, which decreases the activity of mitochondrial complex I triggering the oxidative stress cascade including generation of toxic free radicals and reactive oxygen species (ROS), and resulting in profound dopaminergic-preferring cell death (Przedborski & Jackson-Lewis, 1998). This decrease in activity has been confirmed in PD patients (Parker et al., 1989; Turner & Schapira, 2001). Coenzyme Q10 (CoQ10) is the electron acceptor for mitochondrial complexes I and II, which can increase the activity of complex I, and can decrease oxidative stress (Muller et al., 2003). A randomized, parallel-group, placebo-controlled, double-blind clinical trial evaluated the effects of multiple doses (300, 600, or 1200 mg/day) of CoQ10 in 80 patients with early symptoms of PD. CoQ10 was well tolerated at all doses; however, patients receiving the highest dose of CoQ10 benefited the most among the three doses (Shults et al., 2002). In spite of these promising results, a recent phase III randomized, placebo-controlled, double-blind clinical trial reported no evidence of clinical benefit with high doses of CoQ10 (1200 mg/day or 2400 mg/day) in patients with early PD (The Parkinson Study Group QE3 Investigators, in press). Additional trials are still needed to confirm the role of CoQ10 in slowing the progressive deterioration of function in PD.

2.6.1. N-acetyl-cysteine

N-acetyl-cysteine (NAC) is a thiol antioxidant and a pro-drug of the amino acid cysteine that can systemically deliver cysteine to the brain (Martínez-Banaclocha, 2000). Preclinical studies reported that NAC administration reduced oxidative damage (Martínez-Banaclocha et al., 1999), increased mitochondrial complex I activities (Martínez-Banaclocha, 2000), prevented ROS accumulation (Martínez-Banaclocha, 2012), and protected against dopamine-induced cell death (Offen et al., 1996). A recent clinical trial found that intravenous infusion of NAC increased brain and blood levels of the potent antioxidant glutathione in PD patients (Holmay et al., 2013). Such increases may compensate for the postulated deficiency and lower activity of glutathione in PD (Jenner, 2003). Double blind randomized, placebo-controlled clinical studies with NAC, whether as monotherapy or as add-on to L-DOPA therapy, are still needed to investigate the potential benefits of NAC in improving the symptoms or slowing down the progression of PD (Martínez-Banaclocha, 2012).

2.6.2. Edaravone

Edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one) is a neuroprotective agent used in the neurological recovery of acute brain ischemia and cerebral infarction (Lapchak, 2010). It is a potent antioxidant that scavenges free radicals and protects against oxidative stress and neuronal apoptosis (Shichinohe et al., 2004). Administration of edaravone exerted neuroprotective effects in PD animal model both in vitro and in vivo, although the underlying mechanisms remain to be clarified (Yuan et al., 2008). More recently, edaravone was found to block neurotoxicity in a mutant animal model of PD (Li et al., 2013). Edaravone remains to be evaluated in clinical trials in PD patients.

3. Emerging non-pharmacotherapies

Several non-pharmacotherapies have emerged as adjunctive or alternative approaches for treatment of PD patients. These therapies, however, remain in different stages of preclinical and clinical development, and include the following:

3.1. Viral vector gene therapy

Extraordinary accumulation of genetic findings has identified five "PARK" genes, which can be considered as risk factors for PD. These include α-synuclein [PARK1/4] (Polymeropoulos et al., 1997), parkin [PARK2] (Kitada et al., 1998), DJ-1 [PARK7] (Bonifati et al., 2003), PINK1 [PARK 6] (Valente et al., 2004), and LRRK2 [PARK8] (Paisan-Ruiz et al., 2004). Silencing the over-expression of these genes by using viral vectors such as the lentivirus, adenovirus, and herpes virus as well as polyplexes, may represent a novel therapeutic approach by preventing the progression the disease (Hardy et al., 2006). However, it is essential to evaluate the safety of these vectors to prevent inflammatory responses, which may trigger additional neurodegeneration and worsen the symptoms of PD (Du et al., 1996; McCown et al., 1996).

Viral vectors have been tested in preclinical and clinical studies to assess their potential therapeutic benefits. A study by During and colleagues (2001) infused recombinant adeno-associated virus (AAV) vectors expressing the two isoforms of the enzyme glutamic acid decarboxylase (GAD-65 and GAD-67), the rate-limiting step in γ-aminobutyric acid (GABA) synthesis, into the subthalamic nucleus of aged chronically lesioned parkinsonian rats and reported improvement in spontaneous behaviors and in apomorphine-induced asymmetrical behavior (During et al., 2001). These vectors showed remarkable neuroprotection and were not associated with inflammatory responses (During et al., 2001; Luo et al., 2002). An open label trial evaluated the safety and tolerability of unilateral subthalamic viral vector (AAV-GAD) in 12 patients with advanced PD, and reported significant improvements in motor symptoms 3 months after gene therapy that persisted for up to 12 months. No adverse events related to gene therapy were observed (Kaplitt et al., 2007). These findings suggested that AAV-GAD gene therapy of the subthalamic nucleus was safe and well tolerated by patients with advanced PD. Another proof-of-concept clinical phase 2a trial using an AAV construct designed to deliver the neurotrophic factor, neurturin (CERE-120), to degenerating nigrostriatal neurons showed clinically meaningful benefit in improving quality of life of PD patients 12–18 months after administration compared with the sham surgery control group. Quality of life was measured by Unified Parkinson's Disease Rating Scale (UPDRS), self-report diaries, 7-meter timed walking test (off only), and PDQ-39. No serious safety issues were identified in these patients (Bartus et al., 2013). Nonetheless, the trial failed to meet the primary end point (UPDRS motor-off, measured at 12 months, Bartus et al., 2013).

A recent clinical trial with another vector-based gene therapy reported that bilateral infusion of the lentiviral ProSavin into the putamen of PD patients improved motor symptoms and was safe and well tolerated (Palfi et al., 2014). Current route of viral vector gene administration imposes a significant obstacle that would hinder the wider use of these constructs. In addition, the clinical results with viral vector genes remain preliminary and require further evaluation for their efficacy, safety, and tolerability in PD patients.

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3.2. MicroRNAs

MicroRNAs (miRNA) are a class of small RNAs that consist of 19–23 nucleotides that have a part in post-transcriptional regulation of gene expression (Roshan et al., 2009). These miRNAs essentially guide the cleavage of messenger RNAs (mRNA) and or inhibit their translation, thereby regulating cell cycle. In addition, they also play a role in the differentiation and survival of midbrain dopaminergic neurons (Kim et al., 2007). Molecular studies revealed that one miRNA in particular, miR-133b, was essential for regulating the maturation and function of midbrain dopaminergic neurons (Kim et al., 2007). Animals treated with the neurotoxin 6-hydroxydopamine, or genetically altered mice that lack the expression of a *bicoid*-related homeodomain-containing transcription factor Pitx3 (Pituitary homeobox 3), which is essential for development and differentiation of meso-diencephalic dopaminergic cells (Hwang et al., 2003; Nunes et al., 2003), are deficient in miR-133b (Kim et al., 2007). Accordingly, interventions that can increase the expression of miR-133b and consequently improve differentiation and prolong survival of dopaminergic neurons along the nigrostriatal pathway may prove to have beneficial therapeutic effects for PD patients (Harraz et al., 2011).

Another miRNA that plays a role in PD is miR-433. This miRNA, which is highly expressed in the brain (Davis et al., 2005), binds to one of the two alleles, allele C or allele T, of the single-nucleotide polymorphisms (SNP) rs12720208 associated with fibroblast growth factor 20 (FGF20). FGF20 is considered a risk factor for PD. It can increase the expression of α-synuclein, the main component of Lewy bodies and is thought to be the protein that aggregates and promotes neurodegeneration in PD (Rideout et al., 2003) and in dopaminergic neuroblastoma cells (Wang et al., 2008). It is hypothesized that while the C-allele binds miR-433 tightly and inhibits translation of FGF20, the T-allele inhibits miR-433 and increases the level of FGF20 (Doench & Sharp, 2004). The SNP in FGF20 gene represents an increasing risk factor for PD, but the contribution of this risk factor to the diagnosis and treatment of PD requires further investigation (Wang et al., 2008).

3.3. Transglutaminases

Transglutaminases (TGs) are Ca^{2+}-dependent enzymes that modify various components in the brain via transamidation (Hadjivassiliou et al., 2008; Jeitner et al., 2009). These enzymes are activated by calcium homeostasis disruption, tissue damage, and apoptosis, which typically exist in PD patients (Vermes et al., 2004; Caccamo et al., 2010). Increased activity of TGs catalyzes the formation of α-synuclein crosslinks in substantia nigra of PD patients, which precedes the aggregation of α-synuclein in Lewy bodies (Andringa et al., 2004). Therefore, blocking activity of TGs may slow down the progression of PD. Several agents targeting TGs have been developed. Among them is cystamine, a temporary inhibitor of TG activity (Jeitner et al., 2005), which is effective in blocking transcription and activity of TGs in vitro (Kim et al., 2008; Stack et al., 2008). Other compounds include the reversible TG inhibitors trans-cinnamoyl bensotriazole amides, 3-(substituted cinnamoyl) pyridines [azachalcones] and thieno[2,3-d]pyrimidin-4-one acylhydrazide derivatives (Case & Stein, 2007; Pardin et al., 2008). Nonetheless, all of these compounds remain to be investigated in randomized, placebo-controlled clinical trials enrolling PD patients to determine their efficacy, safety and tolerability.

3.4. RTP801

RTP801 is a proapoptotic gene activated by several factors underlying neurodegeneration in PD such as DNA damage, oxidative stress, and many other energy-depleting mechanisms (Ellisen et al., 2002; Wang et al., 2003; Sofer et al., 2005). The expression of RTP801 gene transcripts was significantly increased in cellular models of PD utilizing the neurotoxin 6-OHDA, as well as in neuromelanin-containing neurons in the substantia nigra of postmortem brain tissue from PD patients (Malagelada et al., 2006), suggesting that RTP801 might be responsible for continued neuronal cell death in PD.

The mechanism by which RTP801 induces apoptosis may involve suppression of mTOR [kinase mammalian target of rapamycin] (DeYoung et al., 2008). As a kinase, mTOR phosphorylates protein kinase Akt, a promoter of neuronal survival (Dudek et al., 1997). RTP801 significantly reduced the phosphorylation of Akt and blocked its neuroprotective effects (Malagelada et al., 2008). Therefore, agents that can inhibit the overexpression of RTP801 or increase the activity of mTOR may be effective in slowing neuronal cell death and delaying the processes of neurodegeneration in PD. One such agent is FLZ, a synthetic squamosamide derivative from a Chinese herb, which improved motor dysfunction in MPTP-lesioned mice (Bao et al., 2012). FLZ appears to increase dopaminergic activity through activation of Akt/mTOR survival pathway and inhibition of RTP801 activity (Bao et al., 2012). Another agent, rapamycin, an allosteric inhibitor of certain actions of mTOR, protected neuronal death in both cellular and animal toxin models of PD by blocking RTP801 activity (Malagelada et al., 2010). However, these two agents still require further evaluation in clinical trials to determine their potential benefits in PD.

3.5. Stem cells

The first clinical stem cell therapy of PD took place in 1987 using aborted human fetal ventral midbrain tissue, and since then more than 400 PD patients have undergone stem cell therapy (Brundin et al., 1987; Nishimura & Takahashi, 2013). In a disease such as PD, where the dopaminergic neurons are progressively lost over time, the goals of stem cell therapy would allow for the replacement of those neurons and for the restoration of normal neuronal sprouting, connectivity and functionality (Geraerts et al., 2007). Several studies reported symptomatic improvement in PD patients after transplantation of these cells (Hallett & Litvan, 1999, 2000), but after two prospective studies in the USA that yielded negative results (Freed et al., 2001; Olanow et al., 2003), these cell lines were abandoned. Failure of these studies may have resulted from difficulties in surgical transplantation of fetal mesencephalic cells, or from non-specific cells within the fetal tissue that could have interfered with cell growth and differentiation (Bjorklund et al., 2003; Freed et al., 2003; Freed, 2004). Post mortem studies revealed that implanted embryonic stem cells are as prone to degeneration as native neurons in the diseased brain area highlighting the need to overcome the obstacle of neuronal degeneration to maintain the efficacy of stem cell therapy (Ren & Zhang, 2009).

3.6. Glial derived neurotrophic factor

Another neurorestorative therapy on the rise is the use of glial derived neurotrophic factor (GDNF). The goal of this therapy is to induce the regeneration of dopamine neurons (Zurn et al., 2001), and GDNF is a particularly fitting target because it was found to enhance dopaminergic cell survival and differentiation (Lin et al., 1993). Chronic infusion of GDNF into the lateral ventricle or the striatum promoted restoration of the nigrostriatal dopaminergic system and significantly improved motor functions in rhesus monkeys modeling advanced stages of PD (Grondin et al., 2002). In addition, GDNF protected nigral dopaminergic neurons from degeneration and improved motor behavior in rats lesioned with the neurotoxin 6-OHDA (Tereshchenko et al., 2014).

Nonetheless, the wider use of GDNF has been limited by the inability of this neurotrophic factor to cross the BBB when administered systemically, triggering the search for novel routes of administration including the use of intra-cerebroventricular catheters implanted directly into the basal ganglia (Gill et al., 2003; Nutt et al., 2003), or through the use of viral vectors (Kordower et al., 2000). These methods have been tested in very small patient populations, which may limit the proper evaluation of the potential benefits of GDNF in improving motor symptoms

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of PD (Gill et al., 2003; Patel et al., 2005; Lang et al., 2006). However, once a safer and non-invasive route of administration that can effectively penetrate the BBB is established, GDNF will become easier to administer and test in a larger population of patients, and it may develop as a more effective PD treatment.

4. Emerging surgical procedures

4.1. Deep brain stimulation (DBS)

DBS is a surgical technique that involves implantation of CT- or MRI-guided electrodes in specific regions of the brain. DBS is used to treat levodopa-responsive symptoms, tremor, on-off fluctuations and dyskinesia, and the typical candidates for this surgery are PD patients with persistent motor symptoms despite optimal medical therapy (Okun, 2012; Favre et al., 2013). The most common areas that receive the implanted electrodes are the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi), both of which are part of the basal ganglia (Okun, 2012). It is postulated that disruption of the firing patterns of STN or GPi would improve motor symptoms of PD by normalizing neurotransmission along the outputs of the basal ganglia (Kandel et al., 2000). An impulse generator creates an electrical current affecting the firing rate, patterning of individual neurons, and neural signaling in the areas closest to the implanted electrodes (Wichmann et al., 2011). It also promotes neurogenesis and an increase in blood flow in stimulated areas (Vedam-Mai et al., 2012). The electric stimuli cause nearby astrocytes to release calcium and neurotransmitters including adenosine and glutamate (Lee et al., 2004, 2011; Tawfik et al., 2010). Despite these chemical, physical, and electrical changes, the exact mechanism of how DBS improves symptoms of PD is not clear (Okun, 2012). A study compared STN versus GPi DBS and reported no significant differences in functional health and composite scores for cognitive, mood, and behavioral effects up to 1 year after surgery between the two targets. However improvements were seen in scales of daily living activities, quality-of-life, and the occurrence of adverse events in the STN group, suggesting that STN could be the preferred target for DBS in patients with advanced PD (Odekerken et al., 2013).

A study by Schuepbach and colleagues (2013) compared the quality of life among early PD patients assigned to undergo subthalamic neurostimulation plus standard medical therapy or medical therapy alone. Patients receiving neurostimulation plus medical therapy showed significant improvements in motor disability, activities of daily living, levodopa-induced motor complications and time with good mobility compared with patients who received medical therapy (Schuepbach et al., 2013). In addition, DBS significantly improved the survival of late-stage PD patients and reduced admittance to long-term care facilities compared to PD patients receiving medical therapy only (Ngoga et al., 2014). Twenty percent of the medical therapy group died from respiratory failure, the most frequent cause of death in PD, compared to 2% in the DBS group (Nobrega et al., 2008; Mehanna & Jankovic, 2010; Ngoga et al., 2014).

Intracranial hemorrhage, infection, and post-operative seizures are the most common adverse events associated with DBS (Voges et al., 2006; Sillay et al., 2008; Coley et al., 2009; Fenoy & Simpson, 2012; Zrinzo et al., 2012). Impairments in gait, balance, and speech have been reported to have less chance of improving and in some cases even worsening. Cognitive impairment, memory deficits, and psychological impairments, including apathy depression, mania, anxiety, panic, and suicidal ideation are other reported side effects (Temel, 2010).

4.2. Pallidotomy

Pallidotomy is a surgical procedure used to reduce motor fluctuations, tremor and dyskinesias by lesioning the GPi postulated to be overactive in PD patients (Okun & Vitek, 2004). The procedure is performed either unilaterally or rarely, bilaterally. High incidences of severe adverse events are associated with bilateral pallidotomy including cognitive impairment, dysarthria, and dysphagia (Merello et al., 2001). A long-term follow-up study in unilateral pallidotomy in advanced PD reported significant improvements in off-period contralateral signs of parkinsonism symptoms including tremor, rigidity, dyskinesia, and bradykinesia five and a half years after surgery (Fine et al., 2000). However, bradykinesia reduction was short term with a gradual recurrence observed at a 10-year follow-up along with an increase in freezing of gait. Despite these motor improvements, reductions in cognitive and executive functions were observed after 5- and 10-year patient follow-ups (Hariz & Bergenheim, 2001; Strutt et al., 2009). Unilateral pallidotomy can also be used as an alternative after stopping DBS due to implanted device infection or worsening dementia and PD symptoms (Bulluss et al., 2013). Despite the decrease in motor complication reduction, the extent of the decrease is not as significant as that reported with DBS with an improvement seen in only the side contralateral to the lesion (Bulluss et al., 2013).

4.3. Thalamotomy

Thermal radiofrequency thalamotomy is an invasive procedure indicated for patients with severe PD and disabling tremor who failed to respond to pharmacotherapy resistant to medical therapy (Nijhawan et al., 2009). It requires the passage of a probe into the brain toward the ventral intermediate (Vim) nucleus of the thalamus, an area involved in the cerebello–rubro–thalamo–cortical circuitry of tremor (Nijhawan et al., 2009). Thalamotomy is performed to lesion the side contralateral to the tremor. Significant improvement in PD symptoms including mobility, tremor, rigidity, emotional well-being, bodily discomfort, and activities of daily living has been reported after unilateral thalamotomy (Valalik et al., 2001; Nijhawan et al., 2009). Since verbal fluency and the task of reproducing a complex geometrical image require a certain level of executive function, it has been suggested that right and left sided thalamotomy may produce disruptions in the neuroanatomical pathways between subcortical areas and the prefrontal cortex, resulting in subtle increased post-operative executive dysfunction (Nijhawan et al., 2009). However, the results of thalamotomy largely depend on the accuracy of locating and destroying a target as well as the size of the lesion.

A more advanced technology developed in 2009 uses transcranial magnetic resonance imaging (MRI)-guided high-intensity focused ultrasound to perform thalamotomy (Martin et al., 2009). A recent study using this procedure reported significant reduction of contralateral hand tremor and disability as well as significant improvement of quality of life 1 year after 15 PD patients with medically refractory essential tremor underwent thalamotomy (Elias et al., 2013). No complications, hemorrhages, or motor deficits were reported. Side effects included paresthesia of lips, tongue, and fingers, head pain, and nausea at a one-year follow-up (Elias et al., 2013). Partly due to surgical procedures and imaging technique advancements, recent studies of stereotactic thalamotomy have shown limited post-operative cognitive impairment (Hugdahl et al., 1990; Lund-Johansen et al., 1996; Fukuda et al., 2000). As targeting and lesion techniques become more advanced, thalamotomy post-operative results will continue to improve.

4.4. Gamma knife

Gamma knife (GK), invented by Lars Leksell (1949), is a noninvasive surgical approach typically utilized in elderly PD patients with persistent tremor, PD patients with medical comorbidities such as cardiovascular diseases that preclude them for undergoing surgical procedures, or patients who want to avoid placement of hardware such as in DBS. In this procedure, patients are fitted with a head frame, and the target within the brain is pinpointed using imaging scans. The patient lies on a bed that slides into the GK machine that emits hundreds of powerful,

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highly focused gamma radiation beams with the beams intersecting at the target. The procedure takes 15 to 40 minutes and typically is performed with local anesthesia (Ohye et al., 2012).

GK procedures have shown to improve tremor, handwriting, and ability to drink in PD patients (Kooshkabadi et al., 2013). The effects of GK procedures take several months to observe as the radiation takes effect to functionally damage or destroy targeted tissue creating a 3–4 mm center of necrosis surrounded by a non-necrotic periphery consisting of astrocytes and hyalinized blood vessels (Kondziolka et al., 2000). A study by Lim and colleagues (2010) found that daily living activities significantly improved in PD patients who underwent unilateral GK thalamotomy (GKT), but no significant improvement was found in resting, postural, action, and head tremor. In contrast, another study reported tremor improvement in PD patients who underwent GKT and completed 24 months of follow-up observations (Ohye et al., 2012). Overall, GK procedures do not have the accuracy seen in invasive surgeries since no intraoperative electrophysiological confirmation of the target site can be validated. This disadvantage has been minimized, at least in part, with the use of improved MRI technology (Kooshkabadi et al., 2013). In addition, a spectrum of potential problems has been associated with this procedure including lesion accuracy and size and the delayed development of neurological complications secondary to radiation necrosis. Accordingly, PD patients should be informed of these potential risks, and should be followed closely postoperatively for any delayed complications (Okun et al., 2001).

4.5. Duodenal administration of levodopa/carbidopa

Levodopa/carbidopa intestinal gel (LCIG, produced by Abbott Laboratories and marketed as Duodopa®) administration is a method developed to minimize the fluctuation in levodopa plasma levels seen in oral administration by providing a continuous influx of steady levels of levodopa (Abbruzzese et al., 2012; Palhagen et al., 2012). This is achieved by using a personal pump to directly administer the LCIG into the duodenum, the main site of intestinal absorption, and therefore bypassing gastric emptying and preventing a suboptimal response to levodopa (Stocchi et al., 2005; Antonini & Odin, 2009). LCIG is approved for use in treatment in more than 30 countries including the European Union, Canada, and Australia, and is currently under review for approval in the USA.

Benefits of LCIG duodenal administration include a significant "off" time reduction and dyskinesia along with a significant improvement in gait disorders and quality of life (Stocchi et al., 2005; Devos & French DUODOPA Study Group, 2009; Merola et al., 2011). One study found that continuous daytime duodenal infusion in PD patients for 6 weeks improved patient outcomes compared with conventional oral tablet treatment. Patients reported fewer difficulties carrying out daily activities and displayed an improved overall functioning and well-being compared with conventional therapy. However, great fluctuation was observed among advanced PD patients when answering questions about walking, being "off," and being hyperkinetic. These traits improved as the day passed and were reported worse during the morning; that was explained by the infusion treatment taking place only during the day. A 6-month follow-up did not show this pattern and is probably explained by a decrease in patient perception while "off" (Isacson et al., 2008). Patients experiencing nighttime symptoms may benefit from 24-hour infusion since pulsatile levodopa plasma levels may contribute to symptoms of "wearing off" and dyskinesia development (Colosimo & De Michele, 1999; Obeso et al., 2000; Nyholm et al., 2005). Maintaining a continuous levodopa level, by one morning and one afternoon infusion, in 7 PD patients for 12 months, significantly reduced dyskinesia and "off" time, compared with baseline, despite unchanged total levodopa doses (Antonini et al., 2007).

The adverse event profile of LCIG is the same as that for oral tablets and is suitable for use in elderly PD patients (Fernandez & Odin, 2011). Complications with the delivery system related to technical and procedural problems may occur including intestinal tube obstruction, infection, or accidental removal of the intestinal tube (Antonini et al., 2007; Abbruzzese et al., 2012).

5. Conclusions

This review has attempted to highlight the most recent advances in the pharmacological and non-pharmacological treatments of PD. Diagnosis of the disease is often complicated and requires careful physical and neurological examinations combined with brain scans to rule out related motor disorders. The current pharmacotherapies offer palliative relief without halting or reversing the progression of the disease. Accordingly, novel therapies are urgently needed to improve the treatment of this neurodegenerative and debilitating disease, the incidence of which is expected to rise substantially as the population ages.

Several emerging pharmacotherapies are in different stages in clinical development to validate their efficacy, safety and tolerability. These include adenosine A_{2A} receptor antagonists, glutamate AMPA receptor antagonists, triple monoamine reuptake inhibitors, monoamine oxidase inhibitors, anti-apoptotic agents, and antioxidants. In parallel, emerging non-pharmacotherapies may offer alternative approaches for treatment of the disease. Most promising is the use of viral vector genes to silence the over expression of defective genes that constitute risk factors for PD. However, the need for direct infusion of these constructs into brain regions of interest has hindered their wider use and limited their potential therapeutic benefits. Stem cell transplants hold great interest as a method to replace dopaminergic neurons lost in PD, though this therapy is faced with many challenges including the identification of the most effective tumor-free cell type to transplant. MicroRNAs, transglutaminases, RTP801 and GDNF have provided promising results in early stages of clinical development. However, additional trials enrolling larger numbers of PD patients are still needed to better understand the neuroprotective or neurorestorative (ability to halt or reverse progression of PD, respectively) effects of these therapies.

Surgical interventions include brain invasive procedures such as deep brain stimulation, pallidotomy, and thalamotomy, or non-invasive procedures such as gamma knife radiation or duodenal administration of levodopa/carbidopa. These interventions are commonly reserved for PD patients with severe disabling symptoms who failed to respond adequately to traditional pharmacotherapies. However, they carry a higher risk of adverse events, and patients should be followed closely postoperatively for any immediate or delayed complications. The combination of pharmacotherapy with surgical interventions appears to have an additive effect that exceeds the benefits of either treatment alone (Hermanowicz, 2001).

Management of non-motor psychiatric symptoms in PD patients remains a challenging issue (Quelhas, 2013). Parkinson's disease psychosis (PDP) is common in patients and contributes significantly to morbidity, mortality, nursing-home placement, and quality of life (Goldman et al., 2011). It mostly occurs as a result of long-term treatment with antiparkinsonian drugs. Adjustment of PD medications or initiation of antipsychotic therapy with agents that carry a lower risk of worsening the motor symptoms such as clozapine or quetiapine is considered as the optimal options of treatment (Wood et al., 2010). A recent clinical trial reported an improvement in PDP with pimavanserin, a novel selective serotonin 5-HT_{2A} receptor inverse agonist. The drug was well tolerated with no significant worsening of motor function (Cummings et al., 2014). Therefore, pimavanserin may provide another option for improved management of PDP. Psychoeducational, behavioral, and therapies employing antidepressant drugs such as venlafaxine, paroxetine, and duloxetine appear to be effective in managing insomnia, depression, and anxiety symptoms in PD patients (Quelhas, 2013).

In conclusion, treatment of PD remains an individualized approach to select the optimal therapeutic intervention for each patient. Several therapies have emerged and may become available for patients in the near future, which will strengthen PD's therapeutic armamentarium.

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The development of disease-modifying agents coupled with advances in imaging techniques and tools to more accurately diagnose the disease in the prodromal phase may prove to be the most successful intervention for preventing the progression of PD.

Conflict of interest

The authors declare that there are no conflicts of interest.

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