Current Pharmaceutical Treatments and Alternative Therapies of Parkinson's Disease

Jie Dong, Yanhua Cui, Song Li and Weidong Le[*]

Center for Translational Research on Neurological Diseases, The 1st Affiliated Hospital, Dalian Medical University, Dalian, China; Collaborative Innovation Center for Brain Science, The 1st Affiliated Hospital, Dalian Medical University, Dalian, China

W. Le

Abstract: Over the decades, pharmaceutical treatments, particularly dopaminergic (DAergic) drugs have been considered as the main therapy against motor symptoms of Parkinson's disease (PD). It is proposed that DAergic drugs in combination with other medications, such as monoamine oxidase type B inhibitors, catechol-O-methyl transferase inhibitors, anticholinergics and other newly developed non-DAergic drugs can make a better control of motor symptoms or alleviate levodopa-induced motor complications. Moreover, non-motor symptoms of PD, such as cognitive, neuropsychiatric, sleep, autonomic and sensory disturbances caused by intrinsic PD pathology or drug-induced side effects, are gaining increasing attention and urgently need to be taken care of due to their impact on quality of life. Currently, neuroprotective therapies have been investigated extensively in pre-clinical studies, and some of them have been subjected to clinical trials. Furthermore, non-pharmaceutical treatments, including deep brain stimulation (DBS), gene therapy, cell replacement therapy and some complementary managements, such as Tai chi, Yoga, traditional herbs and molecular targeted therapies have also been considered as effective alternative therapies to classical pharmaceutics. This review will provide us updated information regarding the current drugs and non-drugs therapies for PD.

Keywords: Cell transplantation, dopamine agonists, gene therapy, levodopa, motor symptoms, neuroprotection, non-motor symptoms, Parkinson's disease.

1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, affecting 1% of the population older than 60 years [1] with the prevalence rates being higher in men than in women at the ratio of 1.6:1 [2]. The classic clinical manifestations of PD include bradykinesia, resting tremor, rigidity and postural instability, which are largely caused by the deficiency of dopamine (DA) in the striatum due to the progressive loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc) [3]. Until now, the exact etiology of PD is largely unknown, but the pathogenesis of PD is believed to be related to reactive oxygen species (ROS), mitochondrial dysfunction, neuroinflammation, and other conditions such as protein degradation failure associated with ubiquitin proteasome system (UPS) and autophagy impairment [4-6]. PD can be divided into idiopathic (90-95%) and familial forms. At least 15 genes are thought to be linked with this disease, some of them have been the hotspot, such as α-synuclein (SNCA), parkin (PARK2, PARK7), leucine-rich repeat kinase 2 (LRRK2), tensin homolog-induced kinase 1 (PINK1) and beta-glucocerebrosidase (GBA) [7].

Clinically, motor symptoms are the main features of PD onset and progression, but non-motor symptoms also could be evident in the early or late stages of the disease, which include neuropsychiatric symptoms such as depression and fatigue, hyposmia, sleep disorders, automatic dysfunction, cognitive impairment and dementia. Since 1960's, treatment for PD has been focused on the replacement or supplement of DA. As the most effective medication in PD treatment, levodopa benefits almost all PD patients [8]. However, long-term use of levodopa is often accompanied by motor complications, including levodopa-induced dyskinesia (LID), "wearing-off" and "on-off" phenomena, which range in severity from mild and non-disabling to incapacitating. Once motor complications emerge, it means that PD patients have entered the advanced stage [9]. Then it is necessary to modify the dosage, change the formulation of levodopa, and combine with DA agonists or other drugs to control the adverse symptoms.

As DAergic neurons degeneration and DAergic dysfunction are responsible for the development of most motor and some non-motor symptoms in PD [10], the current development of new drugs seeks not only to control symptoms, but also to target disease-modifying molecules or pathways to protect and restore DAergic neurons. The latter one includes the current drug treatments, new formulations and feasible alternative therapeutic strategies for PD.

2. SYMPTOMATIC TREATMENTS OF PARKINSON'S DISEASE

2.1. Drug Treatments for Motor Symptoms

Drug treatments of PD motor symptoms mainly comprise DAergic and non-DAergic therapies. The DAergic drugs

*Address correspondence to this author at the Neurology and Director of Center for Translational Research of Neurological Diseases, 1st Affiliated Hospital, Dalian Medical University, Dalian 116021, Liaoning Province, China; Tel: +86-0411-88135850; Fax: +86-0411-88135850; E-mail: wdle@sibs.ac.cn

include levodopa or levodopa plus dopa-decarboxylase inhibitors (DDC-I), catechol-O-methyl transferase (COMT) inhibitors, monoamine oxidase type B (MAO-B) inhibitors and DA agonists. These drugs have been used for decades and show good effects on the motor symptoms of PD. New formulations have been developed constantly due to the limitation of efficiency and the occurrence of side effects of those traditional drugs. In this review, we mainly focus on the new formulations of those traditional drugs and their latest advances.

2.1.1. Levodopa+DDC-I

There is no doubt that levodopa is the most efficient medication for PD. Initially, levodopa offers a stable alleviation of PD symptoms, and is well-tolerated, which called "honeymoon". Nevertheless, there is approximate 40% likelihood of developing motor complications after 4-6 years [11]. Although the mechanisms leading to motor complications are not fully understood, the pharmacokinetics of levodopa, particularly short half-life (ranging from 36-96 min) [12], the emptying and absorption regions, and pulsatile stimulation [13, 14], as well as the disease progression itself are thought to contribute to the occurrence of motor complications.

Once the diagnosis is made, the appropriate time for the introduction of therapy must be considered. PD-MED trial demonstrates that there is very limited benefits of PD patients starting on levodopa treatment earlier versus later [15]. Moreover, Cilia *et al.* present a group of data from a 4-year longitudinal study, which indicate that motor complications are most likely to be correlated with a higher levodopa daily dose and longer disease duration [16]. Thus, it seems unwise to withhold the use of levodopa because of the motor complications.

Pulsatile stimulation, due to the short half-life and rapid catabolism of DA, leads to intermittent delivery to receptors [17]. It is suggested that continuous DAergic stimulation may delay or even reverse the motor complications [14, 18]. The formulation of levodopa and DDC-I (benserazide and carbidopa are currently used) is aimed at reducing peripheral levodopa degradation and subsequent DAergic side effects [19-21]. Melevodopa, the methyl ester of levodopa, can improve daily motor performance, especially in patients with both "delayed-on" and "wearing-off" [22].

Several new formulations of levodopa have been developed to provide a more stable levodopa plasma concentration, most of which are able to reduce off-time and levodopa use frequency, or increase on-time without troublesome dyskinesia (Table **1**). IPX066 is an extended-release formulation of levodopa/carbidopa (LD/CD). A phase 3 study of IPX066 conducted at 68 academic and clinical centers reports that IPX066 has a greater reduction in daily off-time by extra 1.17h than immediate-release LD/CD [23]. DM-1992, a bilayer formulation combining both immediate and extended-release gastroretentive LD/CD, shows a significant reduction in off-time by 5.52% and exhibits a smoother plasma levodopa concentration profile [24].

Different delivery methods such as intestinal and continuous subcutaneous infusion, inhalable formulation and intravenous delivery can achieve the similar goal of optimizing dose and reducing side effects. Unfortunately, although intravenous delivery results in stable plasma concentration and reduces motor fluctuations, it has the risk of causing thrombosis; therefore, it can not be used for long term treatment [25]. LD/CD intestinal gels (LCIG), after a percutaneous gastrojejunostomy, provide a good tolerability profile and reduce the severity of motor fluctuations and LID, which may offer a promising option for controlling motor complications [26, 27]. Among other investigational products, CVT301, a formulation to deliver large dose, can achieve a therapeutic concentration in 5-10 minutes [28]. Besides, nasal powder formulations of melevodopa may provide a better brain-targeting delivery route than those oral formulations [29].

2.1.2. COMT Inhibitors

COMT is an enzyme for peripheral metabolism of levodopa. Its inhibitors are always used in triple combination with levodopa and carbidopa, which has become a first line medication for motor fluctuation treatment of PD. Entacapone can lead to an improved motor fluctuation, with 1.0-1.7h more on-time and less off-time per day [42]. Stalevo®, a tablet consist of LD/CD and entacapone, can provide a more stable plasma levodopa level and a persistent stimulation of DA receptors in the striatum [43]. However, the recent FDA Adverse Event Reporting System (FAERS) database warns that there is a risk of death with the use of an entacapone-containing drug combination, and it requires more epidemiological studies to confirm its safety [44].

Nebicapone, a more effective COMT inhibitor than entacapone, has been under phase 3 clinical trial. It reduces off-time approximate 100 min with nebicapone of 150 mg compared to 70-80 min with entacapone of 200 mg [45, 46]. The third generation of COMT inhibitor, opicapone (OPC) shows a potent effect by increasing levodopa exposure (AUC) 65.6% with 30 mg without inducing toxicity [47, 48].

2.1.3. MAO-B Inhibitors

MAO-B plays an indispensable role in DA metabolism in the brain. It can be used as monotherapy in early stage or combination with levodopa. Selegiline, the first MAO-B inhibitor used in PD, delays the need for levodopa by slowing the progression of PD [49, 50]. Switching selegiline to rasagiline can improve motor behavior, motor complications, mood and sleep disorders due to the additional glutamate receptor antagonizing properties of rasagiline [51].

Safinamide (Xadago®) has just been approved globally. This drug can effectively inhibit MAO-B and excessive glutamate release, and selectively modulates sodium channel and calcium channel, *via* both DAergic and non-DAergic mechanisms [52]. In a 2-year, double-blind, randomized-controlled trial (RCT), safinamide at 50 or 100 mg/day dose provided significant clinical benefits in on-time without causing troublesome dyskinesia [53]. Another phase 3 multicentre research also demonstrates a significant increase in total on-time, which is about 1.36 hours with safinamide at 50 or 100 mg/day [54].

Table 1.   Different formulations of levodopa+DDC-I.

Formulations	Mechanisms	Study Phase	Characteristics	Refs.
LD/CD or LD/benserazide	LD+DDC-I, reduce peripheral elimination	Registered drug	Increase in bioavailability by approximately 100%; reduce peripheral side effects	[19-21]
LCIG	LD/CD intestinal gel	III	Stable plasma levodopa concentrations; reduce motor symptoms and complications	[26, 27, 30, 31]
melevodopa	levodopa methyl ester with high solubility	Registered drug	Improve motor symptoms and quality of life; reduce motor fluctuations (optimization of morning delay on and afternoon off periods)	[22, 32, 33]
IPX066	extended-release LD/CD	III	Stable levodopa plasma level (a longer duration of time with > 50% of peak dose); reduce off-time and dosing frequency than immediate-release LD/CD	[23, 34, 35]
accordion pill	prolonged gastric retention of LD/CD	II	Reduce off time and increase on time without troublesome dyskinesia compared with LD/CD	[36]
DM1992	combining immediate and extended-release gastroretentive LD/CD	II	Reduce off time compared with immediate-release LD/CD; reduce dosing frequency; elevate predose plasma levodopa concentration	[24]
ND0612	continuous subcutaneous LD/CD	IIa	Stable levodopa level; reduce motor fluctuations compared with oral levodopa; well-tolerated	[37]
CVT301	inhalable levodopa	III	Study ongoing	[28]
ODM-101	levodopa + carbidopa (65/105mg)+entacapone	II	Reduce daily off time; increase daily on time without troublesome dyskinesia	[38]
stalevo	LD+CD+COMT inhibitors (entacapone)	Registered drug	Increase motor and daily activities; reduce severity of basic symptoms and improve quality of life	[39]
XP21279	extended-release levodopa prodrug	II	Greater reduction in off time; increase levodopa plasma concentration; decrease plasma level variation.	[40]
IPX054	bilayer tablet of immediate and extended-release LD/CD	II	Reduce dosing frequency of standard LD/CD	[41]

Because of the first-pass effect, the oral bioavailability of selegiline is only 10% [55]. The orally disintegrating tablet (ODT) can improve the bioavailability effectively and reduce dose significantly [56, 57]. Recently, preclinical trials of novel delivery systems of rasagiline are also reported to be effective, such as nanoparticals through intranasal route and transdermal system [58-60]. However, transdermal application of selegiline is mostly used for major depressive disorders, not routinely for PD treatment [61].

2.1.4. DA Receptor Agonists

DA receptor agonists, as initial monotherapy or adjunct treatment for PD to improve motor fluctuations, are commonly used medications for PD. Adverse effects of DA agonists include hallucinations, hypotension, nausea, vomiting, pathological gambling, compulsive shopping and hypersexuality [62].

Ergot derivatives are seldom used now due to severe side effects of valvulopathy and pleuropulmonary fibrosis [63-65]. Non-ergot derivatives include ropinirole, pramipexole, rotigotine and apomorphine. According to a meta-analysis study, non-ergot derivatives exhibit similar improvements in

motor score and off-time [66]. Pramipexole with high affinity of D3 receptor is able to alleviate LID to certain extent [67]. Rotigotine transdermal patch, providing continuous drug delivery over 24h, shows improvements in off-time [68-70]. Apomorphine, a short-acting D1/D2 receptor agonist, has two delivery formulas (intermittent injections and subcutaneous infusions). In addition, it can also be used as inhaled dry powder and sublingual strip, which are still under clinical trials [71-73]. Apomorphine is usually used to reduce off-time without obvious dyskinesias improvement. The comprehensive introductions of novel formulations of DA agonists under preclinical or clinical trials are summarized in Table **2**.

2.1.5. Anticholinergics

Antagonism of muscarinic acetylcholine receptors aids in the correction of the imbalance between DA and acetycholine. Anticholinergic drugs such as benztropine, trihexyphenidyl have been registered by FDA. It is one of the M4 receptor antagonists among the whole 5 subtypes of muscarinic acetylcholine receptors (M1-M5), and they are often used in tremor treatment [82, 83]. Clinical use of anticholinergics is limited due to the obvious adverse effects, which even outweigh therapeutic benefits to some extent.

Table 2.   New formulations of DA agonists.

Formulations	Mechanisms	Study Phase	Refs.
KW-6500	Subcutaneous infusions of apomorphine	III completed	[74]
Pramipexole ER	Extended-release pramipexole	III completed	[75]
APL-130277	Sublingual apomorphine	III	[76]
Aplindore	High affinity, dopamine D2 receptor partial agonist	II	[77]
S90049	Sublingual formulation of the non-ergoline D2-D3 agonist piribedil	IIa	[78]
VR040	Nasal inhalation of apomorphine	IIa	[79]
RH-CSNPs	Intranasal delivery of ropinirole	preclinical trials	[80]
SOMCL-171	Dopamine D2 and serotonin 5-HT1A dual agonist	preclinical trials	[81]

According to a logistic regression study in 1636 elderly patients, the significant risk of using anticholinergics includes immobilization, urinary dysfunction, disorders of digestion and neurologic and psychiatric comorbidities, such as depression, PD, and epilepsy [84]. Anticholinergic drugs also lead to blurred vision and tachycardia. From a multivariate analysis, anticholinergics application is correlated to the decline of all the activities of daily life, higher rate of falls and delirium, and gait freezing [85, 86]. Thus, PD patients who comorbid dementia should avoid using anticholinergics [87].

2.1.6. Amantadine

Amantadine is originally introduced as an antiviral medication. It is accidently found that the drug is able to relieve PD early symptoms [88]. Antidyskinetic effects of amantadine are confirmed by abundant evidences. Many clinical trials have demonstrated that amantadine could reduce the duration of LID and freezing severity, and improve daily activities in PD [89, 90]. There is a remarkable improvement of unified Parkinson's Disease Rating Scale (UPDRS)-IVa in amantadine-treated patients than those placebo-treated controls [91]. It improves parkinsonian symptoms, mostly balance and gait [92, 93]. Moreover, amantadine also shows the effect to reduce pathological gamble, the adverse effect from DA agonists [94]. However, withdrawing amantadine may cause a worsen LID in 7 days and induce a rebound of 10-20% increase in dyskinesia, thus a gradual amantadine withdrawal is necessary for routine clinical practice [95, 96].

2.1.7. New Drugs Outlook

Cannabis is one of medical marijuana. In a small controlled trial, at 30 min after smoking cannabis, there was a remarkable alleviation in tremor, bradykinesia and rigidity. This might be an alternative therapy for PD, but it still requires verification through additional studies with larger sample size [97].

Recently, Wright and colleagues have synthesized a small molecule angiotensin IV ligand-based compound, which could bind to angiotensin 4 receptor to facilitate compromised memory and motor systems [98]. Although

this compound is still in the preclinical trials, it shows high promise in PD motor symptomatic treatment improvement.

2.2. Drug Treatments for Non-motor Symptoms

Now, the significance of non-motor symptoms has been recognized due to the greater negative influence on quality of life compared with motor signs. Patients experience a wide range of non-motor symptoms, including cognitive impairment, neuropsychiatric disturbances, sleep disorders, autonomic dysfunctions (gastrointestinal, cardiovascular, urinary, thermoregulation) and pain syndrome [99].

2.2.1. Cognitive Impairment

Cognitive impairment can be developed from mild cognitive impairment (MCI) to PD dementia (PDD). The possibility of developing dementia increases along with the PD progression that consists of approximately 50% incidence rate after 10 years and 80% after 20 years of the disease [100, 101]. Given that the underlying mechanisms remain unclear, there is no mechanism-based treatment available now. A multidisciplinary approach and accurate communication with patients and relatives are essential [102].

Rivastigmine, butyrylcholinesterase and acetylcho-linesterase dual inhibitor, is available in two formulations, oral capsules and transdermal patch, of which transdermal patch may improve tolerability of gastrointestinal adverse effect and has more practical advantages than oral capsules [103]. Donepezil is a selective acetylcholinesterase inhibitor. One recent phase 3 trial has demonstrated that long-term donepezil administration at 5 or 10 mg/day can improve cognitive function without increasing risk [104, 105]. Memantine is used commonly in clinical practice, but a recent meta-analysis and trial sequential analysis indicate that both memantine and cholinesterase inhibitors including rivastigmine and donepezil produce slight efficacy on impression change, but only cholinesterase inhibitors can enhance cognitive function, not the memantine [106].

2.2.2. Sleep Disorders

PD patients experience a wide range of sleep disorders, such as insomnia, excessive daytime sleepiness, restless legs syndrome and REM-sleep behavior disorder (RBD) [107].

However, the effects between PD and sleep are mutual which reflects the high risk of developing to MCI/PD in RBD patients [108].

Based on clinical practice, clonazepam is considered as the first line therapy for RBD. A comparative RCT study suggests that both clonazepam and melatonin could reduce sleep disorders, while melatonin treatment offers higher scores in Mini-Mental State Examination, five-word test, and Hamilton scale than clonazepam-treated group. However, the daytime sleepiness can be significantly increased by clonazepam [109]. Several RCT studies have demonstrated non-ergot DA agonists such as piribedil, rotigotine and LD/CD preparation are able to reduce daytime sleepiness and improve sleep as well [110-113]. Doxepin, as a medication against depression, is confirmed by a small scale randomized study to produce an improvement in sleep [114]. Besides, rivastigmine can significantly decrease the frequency of RBD episodes [115]. Several researchers have suggested homotaurine or cannabis could be alternative therapies for sleep disorders, but this notion still requires further studies for confirmation [97, 116].

2.2.3. Depression

Recent two meta-analyses have shown that antidepressants have moderate but non-significant pooled effect in PD, and insufficient evidence to support selective serotonin recapture inhibitors (SSRIs), pramipexole, pergolide and norepinephrine recapture inhibitors (SNRIs). Tricyclic antidepressants (TCAs) might be the most effective medication for depression treatment followed by pramipexole, SNRIs and SSRIs [117, 118].

In an exploratory post hoc analysis, patients are divided into rasagiline-treated and placebo groups. It turns out rasagiline-treated group has a significantly less worsening depression scores [119]. In addition to pharmaceutical treatments, the cognitive behavioural therapy seems to be efficacious and practical [120]. Although there are several drugs to choose, we still have no standard guideline to follow.

3. NEUROPROTECTIVE TREATMENTS OF PARKINSON'S DISEASE

Neuroprotection is one of the disease-modifying therapies in PD. It would produce benefits for patients through blocking the disease process or underlying pathogenesis, aiming at the improvement of mitochondrial function, prevention of α-synuclein dysregulation and stimulating neurotrophic factors production [121]. Different approaches need to be applied in different stages of PD. Among them, antioxidants, including green tea polyphenol, glutathione, nicotine, iron chelators, melatonin and polydatin, account for a large proportion and are gaining increasing attention [122, 123]. The clinical trial outcomes of these neuroprotective drugs for PD treatment are listed in Table **3**.

Importantly, while most neuroprotective drugs show robust improvement in animal models, few have been turned out to be effective in clinical trials [148]. Several commonly used non-prescribed medications such as coenzyme Q10 and creatine are of no proven clinical benefit according to recent studies [149, 150]. The failure of clinical trials of neuro-

protective drugs may be resulted from the following three causes. Firstly, most positive outcomes of neuroprotective compounds are based on toxin-induced acute animal PD models. Transgenic parkinsonian models may be better choices to mimic chronic pathogenic process of PD. Secondly, the recruited patients are mostly in the late stage of disease, therefore we are not able to evaluate the long-term outcomes of these drugs. The early diagnosis of PD is still a big challenge due to the lack of appropriate biomarkers. Thirdly, the outcomes of these neuroprotective drugs are mainly estimated by motor scores, imaging manifestations of DA transporters or the abosorptivity of ^{18}F-dopa, without direct observation of pathological or physiological manifestations. Thus, these problems are urgently needed to be solved in order to make a better evaluation of neuroprotective drugs of PD.

3.1. Rasagiline and Selegiline

MAO-B inhibitors, rasagiline and selegiline, can stabilize mitochondria membrane permeabilization through inhibition of Ca^{2+} efflux to suppress activation of subsequence apoptosis cascade and induce brain derived and glial cell line derived neurotrophic factors (BDNF and GDNF) [151]. In animal experiments, rasagiline is more potent than selegiline in both neuroprotection and neurorestoration [152]. The ADAGIO study is registered to test the disease-modifying effects of rasagiline, indicating that rasagiline at 1 mg not 2 mg/day has benefits against PD progression [144]. Selegiline can play a similar role as rasagiline in delaying disease progression after a long-term usage [50].

3.2. Ropinirole and Pramipexole

Ropinirole and pramipexole are D2/D3 receptor agonists. Pramipexole can increase the levels of several neurotrophic factors and induce autophagy in UPS-impaired animals [153]. Ropinirole can inhibit the subsequence apoptotic cascade and block the Ca^{2+} transition of mitochondria [154]. SPECT/PET imaging shows pramipexole and ropinirole could reduce the DAergic neuron degeneration and slow PD progression compared with levodopa [145, 146]. However, a recent phase 4 trial suggests that pramipexole does not have neuroprotective effect [147].

3.3. Glutathione

Given that oxidative stress is one of the pathogenetic factors in PD, glutathione, as the primary antioxidant in the brain, can deplete excessive ROS formation and supply a promising therapy for PD. Because glutathione cannot pass the blood-brain-barrier directly, the intranasal delivery system is developed that can bypass the obstacle. The safety, tolerability and absorption data of intranasal glutathione is being evaluated [130]. N-acetylcysteine is regarded as potential precursors of glutathione. It can produce a dose-dependent increase of glutathione concentrations in the brain [125,155].

3.4. Green Tea Polyphenol

Much epidemiology evidence indicates drinking green tea has the potential to protect or reverse neurodegeneration

Table 3.   Clinical trial outcomes of neuroprotective drugs for PD treatment.

Medications	Mechanisms	Study Phase	Status	Outcomes	Refs.
N-acetylcysteine	Antioxidant	I	Completed	Increase glutathione level in the brain	[124]
		I/II	Ongoing		[125]
Green tea polyphenol	Antioxidant, iron chelator	II	Inconclusive		[126]
Nicotine	Unfolded protein inhibitor, calcium handling	II	Completed	Improve motor scores and reduce medicine dosage	[127]
		II	Ongoing		[128]
Glutathione	Antioxidant	I	Completed	No significant symptomatic improvement	[129]
		IIb	Inconclusive		[130]
Granulocyte-colony stimulating factors	Anti-apoptotic, neurogenesis induction, immunity modulation	II	Inconclusive		[131]
Deferiprone	Iron chelator	II/III	Completed	Early-start patients respond earlier to medicine; slow disease progression compared to delayed-start group	[132]
Isradipine	Calcium channel antagonist	II	Completed	Isradipine 10 mg/d was the maximal tolerable dosage and the common side effects are edema and dizziness	[133]
		III	Ongoing		[134]
Coenzyme Q10	Antioxidant	III	Completed	Safe but no evidence of benefit	[149]
		III	Completed	Safe but no evidence of benefit	[135]
Recombinant human erythropoietin (EPO)	Anti-inflammation, antioxidant	II	Completed	Improve non-motor symptoms, not the motor symptoms	[136]
		III	Completed	Improve both motor and non-motor symptoms	[137]
Creatine	Ergogenic compound	II	Completed	Nonfutile and well-tolerated	[138]
		II	Completed	Safe; not interfere with symptomatic treatment	[139]
		III	Terminated	No evidence of benefit for 5-year follow up	[150]
Minocycline	Anti-inflammation	II	Completed	Nonfutile but tolerability is only 77%	[138]
		II	Completed	Nonfutile, safe but with progressively decreased tolerability	[139]
Exenatide	Glucagon-like peptide-1 mimetics	II	Completed	Improve both motor and non-motor functions and well-tolerated	[140]
		II	Ongoing		[141]
GPI 1485	Nonimmunosuppressive immunophilin ligand	II	Completed	Nonfutile	[142]
Rasagiline	MAO-B inhibitor (antioxidant/ antiapoptotic)	III	Completed	Rasagiline with 1 mg would provide disease-modifying effect	[143]
		III	Completed	A significant difference between early-start and delayed-start groups with rasagiline 1 mg	[144]
Selegiline	MAO-B inhibitor (antioxidant/ antiapoptotic)	III	Completed	Delay the start of PD symptoms	[50]
Ropinirole	D2/D3 receptor agonist	III	Completed	Slow the loss of DA neurons	[145]
Pramipexole	D2/D3 receptor agonist	III	Completed	Slow the degeneration of DA neurons	[146]
		IV	Completed	No significant difference between early-start and delayed-start groups	[147]

disorders including Alzheimer's disease and PD. (-)-Epigallocatechin-3-gallate (EGCG) is the main extraction from green tea. The neuroprotective mechanisms of EGCG are mostly related to its antioxidant, iron chelator and neuritogenic properties [156]. In a double blind RCT, a total of 480 PD patients are divided into three dosage groups of EGCG to evaluate its effectiveness by a delay start design, while the result has not been published yet [126].

3.5. Nicotine

Nicotine, the tobacco-derived compound, is considered beneficial to PD. Some nicotine's derivatives diminish oxidative stress and neuroinflammation and improve DAergic neurons survival [157]. In a small-scale trial, high dose and chronic treatment with transdermal nicotine improved motor scores and reduced DAergic usage [127]. A previous study has suggested the potential neuroprotection of nicotine may attribute to the deceleration of the decrease binding potential of DA transporters [158]. To confirm the neuroprotective effect of transdermal nicotine, PD patients are applied with nicotine at 7 to 28 mg/day or placebo for 52 weeks. This phase 2 trial has been verified at November 2014, and is currently recruiting new patients [128].

3.6. Granulocyte Colony Stimulating Factors

Granulocyte colony stimulating factor (G-CSF) has been used for hematologic disorders treatment routinely for decades. In rodent experiments, it is found that motor performance improvement is relevant to the preservation of nigrostriatal pathways [159]. Currently, a two-year clinical trial is designed to evaluate the disease modifying effect of G-CSF on early PD. Patients are divided into three arms, high and low dose of G-CSF and placebo group, while the outcome is still unknown [131]. Intravenously delivery is the most common method of G-CSF application. Recently Heinzelaman and colleagues found that some bioactive variants might make oral administration possible [160]. If it is successful in clinical trial, it would be a big step for the clinical application of G-CSF in PD.

3.7. Iron Chelators

There is an abnormal aggregation of labile iron, ROS and ubiquitin-conjugated proteins in PD patients [161]. The role of an iron chelator is to reduce oxidative stress damage, which is associated to regional iron deposition. For a pilot, double blind RCT with deferiprone, early-start PD patients respond significantly better than delay-start PD patients [132]. Recently, Bar-Am O has just synthesized a novel iron chelator VAR103039 (VAR), which can permeate through the brain. It possesses both anti-peroxidation potency and MAO inhibitory effects. After treatment with VAR, PD rat model shows a reduction of striatal DAergic neurons loss, together with increased neurotrophic factors expression and an ameliorated cognitive impairment [162].

3.8. GLP-1 Mimetics

Glucagon like peptide-1 (GLP-1) mimetics initially synthesized to treat diabetes shows good effects in several PD models. Based on numerous observations, GLP-1 mimetics may have biological effects against the progression and pathogenesis of PD. In animal models, GLP-1 mimetics exenatide preserves DAergic neurons from degeneration [163]. Furthermore, a small cohort study of exenatide has been conducted. Patients who receive exenatide randomly for 1 year show a significant improvement of motor and non-motor scales, even during the 2-month drug washout period [140]. To test whether exenatide has neuroprotective function or not, a phase 2 trial with bigger scale and longer time has just been verified at March 2015 [141].

4. SURGICAL, GENE AND CELL REPLACEMENT THERAPIES FOR PARKINSON'S DISEASE

4.1. Deep Brain Stimulation (DBS)

DBS has generally been accepted as an alternative therapy for PD. Subthalamic nucleus (STN) and globus pallidus internus (GPi), two most hyperactive regions during PD progression, are usually used as targets for DBS. The underlying mechanism for DBS still remains poorly understood. Recently, the "disruption hypothesis", which declares DBS dissociates both input and output information and blocks unusual signals through the cortico-basal ganglia loop, seems to be more and more accepted [164]. After long-term observation, both STN and GPi-DBS showed significant improvement in "on-off" conditions, dyskinesias, and motor fluctuations [165, 166]. Although the efficiency of STN and GPi-DBS shows no difference in primary outcome, STN-DBS could be preferred in advanced PD stage due to the big improvements in off time [167]. Recently, low frequency around 60 Hz of DBS shows a promising application potential to improve swallowing, gait freezing, and axial motor signs, almost overall motor signs of PD [168, 169]. Additionally, a new approach, directional steering of DBS, brings more potential benefits *via* widened therapeutic window and increased effectiveness [170]. However, the effects of DBS on cognitive and psychiatric symptoms of PD have been controversial. A progressive worsening of neuropsychological performance is observed in a follow-up study of DBS [171]. Some scholars consider that the impairment of neurocognition may attribute to the disease progress and medication reduction, not the DBS itself [166, 172, 173]. Interestingly, in preclinical studies, there is an improvement of DAergic neurons survival and an increase of BDNF level in the SN and primary motor cortex after STN-DBS exposure, suggesting the neuroprotective effects of DBS [174, 175].

4.2. Gene Therapy

In general, gene therapy requires a vector and a carried gene. The latter includes glutamic acid decarboxylase (GAD), aromatic L-amino acid decarboxylase (AADC), neurturin, neurotrophic factors and others. A recent phase 1/2 trial with one-year follow-up of ProSavin has shown that ProSavin therapy can result in a significant improvement in UPDES III scores without serious side effects [176]. Transfer of GAD with adeno-associated virus type 2 (AAV2) can modulate GABA production with a great improvement of UPDRS scores over 6 months as well [177]. Others like AAV2-hAADC and AAV2-neurturin (CERE-120) also show similar therapeutic effects and safety profiles [178-180]. Moreover, novel vectors are developed constantly. Tropism-

modified Ad5 vectors are just synthesized, which have neuron-selective targeting property to enhance gene delivery efficiency [181]. Besides, angiopep-conjugated nanoparticles for cellular uptake and gene expression can carry specific genes without viral vector [182].

4.3. Cell Transplantation

Cell transplantation has been used for decades and several clinical trials have shown therapeutic effects of stem cell transplantation, such as improvement of motor signs or reducing medicine dosage [183, 184]. Transplantation of stem cells-derived DAergic neuron can alleviate motor deficiencies of PD, but whether it would result in uncontrolled cell proliferation still remains concern. To avoid tumor formation, Acquarone *et al.* pretreated undifferentiated mouse embryonic stem cells (mESCs) with mitomycin, then injected into striatum in nude mice. After 15 months follow-up, it is found that DNA alkylating agent mitomycin-treated mESCs can alleviate motor functions dramatically without unlimited cell proliferation that would be a novel replacement therapy for PD [185]. Besides, reprogrammed neurons, such as combination of new transcriptional therapy may decrease the tumorigenic potential [186]. Using human unfertilized cell or pluripotent stem cells (iPS cells) also offers an unlimited supply for transplantation. Several animal experiments confirm its safety and efficiency on motor symptoms [187, 188]. In a long-term 14-year observation after DAergic neuron transplantation, it is reported that the majority of transplanted neurons maintain healthy and functional, as shown by persistent expression of DA transporters and normal mitochondrial morphologies, which proves the rationality and feasibility of cell transplantation in PD treatment [189].

5. COMPLEMENTARY & ALTERNATIVE MANAGEMENT OF PD

Complementary and alternative management of PD means a group of therapies or products, other than the classical and well-accepted therapies, that can assist the treatment of PD. The variety of alternative management is increasing yearly, mainly including Tai chi, Qi gong, yoga, massage, acupuncture, dance, traditional herbs, molecular targeted therapies and near-infrared light (NIr).

5.1. Exercise

In the last two decades, exercise, as a supplementary approach for PD treatment, has caused clinical interests due to the amelioration of both motor and non-motor symptoms and its neuroprotective effect. It alleviates motor deficits through increasing mitochondrial respiration and stimulating neuroplasticity [190]. Moreover, the latest study claims the recovery of DA and glutamate transporters, plus suppression of inflammation may be involved in the mechanisms as well [191]. Exercise is an effective complimentary therapy that shows promise, but it needs more long-term and follow-up studies to evaluate its effectiveness.

5.1.1. Conventional Physical Exercises

Recent clinical trials have suggested aerobic exercise including aerobic walking and stretching could ameliorate motor functions such as gait, balance, physical performance, and non-motor functions such as fatigue, depression and cognition, but not for fall prevention in PD patients [192, 193]. It has been reported that intensive training modalities could improve muscle strength and mobility [194, 195].

5.1.2. Tai Chi and Qi Gong

Compared with conventional physical exercises, Tai Chi, a traditional Chinese exercise combining with deep breath and slow movements, has been proved effective in reducing balance impairment and falls [196, 197]. According to the recent meta-analysis, Tai Chi shows positive effects in motor function and balance, but not in gait velocity, step length and gait endurance improvements [198]. Tai Chi is a safe and feasible exercise that improves quality of life, and it could be a good exercise strategy for PD patients with mild to moderate severity.

Qi Gong is a traditional exercise like Tai Chi but focuses on the transfer of internal energy. One RCT has suggested that Qi Gong could improve UPDRS-III scores, together with several non-motor symptoms amelioration [199]. But another small-scale RCT demonstrates that there is no significant motor benefit in Qi Gong [200]. Therefore, it still needs more studies to explore whether Qi Gong is beneficial to PD or not.

5.1.3. Yoga

Yoga is a popular discipline that origins from India. It significantly improves flexibility, strength, gait and quality of life. One pilot study has shown that yoga improves UPDRS scores, immediate tremor and some physiological functions [201]. Another pilot study demonstrates that after an 8-week yoga program, some texts such as sit-and-reach text, single-leg balance text are improved significantly, and depression is alleviated to some extent [202]. Until now, there is still no big-scale RCT about yoga in PD treatment. It requires larger population of individuals to participate in the clinical trial in order to ascertain the efficiency of yoga for PD patients.

5.1.4. Dance

Dance as an intervention for PD patients could improve both motor and non-motor symptoms. The recent meta-analysis suggests that short-term dance significantly improves UPDRS scores, balance and gait as compared with no intervention [203]. Dance, especially Tango, has been reported to alleviate motor function and balance, as compared with common exercise [204].

5.2. Massage and Acupuncture

Massage is one common complementary therapy for PD. According to a small scale study with 10 patients treated with Japanese massage for 2 months, it shows a positive effect in various symptoms, such as shoulder stiffness, muscle pain and fatigue [205]. Another study also suggests that after 40-minute Anma massage, patients' movement difficulties are generally improved [206].

Acupuncture has been a vital part of Chinese medicine for thousand years. Bee venom acupuncture is popular recently to treat pain and arthritis, which may attribute to anti-inflammatory effect. A recent randomized trial has demonstrated that after 8-week intervention, both acupuncture and bee venom acupuncture could improve UPDRS scores of PD patients [207]. In another randomized trial, patients are divided into acupuncture, covert placebo and overt placebo groups to evaluate the effect of acupuncture and placebo and found that acupuncture brought significant improvement of motor function with putamen and primary motor cortex activation [208]. Placebo could also activate some brain regions that are not vital for basal ganglia-thalamocortical circuit. Acupuncture seems to be a promise alternative therapy for PD.

5.3. Traditional Herbal Medicines

Herbal medicines have been used for thousand years, and recent studies have suggested some of them are able to alleviate PD symptoms. One pilot study reports that dietary extract rikkunshi-to could reduce gastroparesis in terms of shortening gastric emptying time in PD [209]. Yokukansan is another kind of herbal extract, which is efficient in ameliorating neuropsychiatric symptoms, such as hallucinations, anxiety and apathy, according to a small-scale exploratory trial [210]. Through evaluating neurotransmitters in the brain, Bushen huoxue formulas are found to enhance the levels of 5-HT, DA and HE, and to improve the depression of PD [211]. In another RCT about Bushen huoxue formulas, it could improve UPDRS scores and relieve muscle tension [212]. In addition, a multicenter RCT of 320 PD patients is recently underway in China to investigate the efficacy and safety of a Chinese herbal medicine, Xifeng Dingchuan Pill, which is thought to delay the progression of PD and improve quality of life [213].

5.4. Molecular Targeted Therapies

With the disclosing of more molecules that are involved in PD pathogenesis, regulation of these PD-related molecules seems to be attractive to provide novel disease-modifying strategies. Until now, a series of preclinical trials targeting kinases such as leucine-rich repeat kinase 2 (LRRK2), glycogen synthase kinase 3 beta (GSK-3β), cyclin-dependent kinase 5 (Cdk5), α-synuclein and transcription factors such as MEF2, nuclear factor erythroid-2-related factor 2 (Nrf2) and Nurr1 [214-220] have been demonstrated to be effective in PD treatment.

LRRK2 mutations are the common genetic cause of familial and sporadic PD. LRRK2 inhibitors have been actively investigated in recent decades and dozens of patent applications have been published [221]. Remarkably, there is only one clinical trial until now to apply LRRK2 inhibitor into human subjects [222], and the toxic tolerance and side effects of the LRRK2 inhibitors remains unknown [223]. In addition to LRRK2, GSK-3β is also involved in PD pathogenesis. It plays an important role in controlling neuroinflammation and neuronal apoptosis, and the inhibition of GSK-3β decreases the level of α-synuclein. Abundant evidence has shown that GSK-3β inhibitors could reduce the loss of DAergic neurons and the expression of pro-

inflammatory factors in PD animal models [224, 225]. GSK-3β inhibitor tideglusib has been estimated in clinical trials for treating progressively supranuclear palsy [226]. We believe that it would not be far away from the clinical applications of GSK-3β inhibitors to treat PD. Besides, immune therapies targeting α-synuclein such as active and passive antibodies have shown good results in alleviating the pathological changes and behavioral symptoms in preclinical investigation [220]. Recently, several studies have suggested that transcriptional factor Nurr1 is a promising therapeutic target for PD. Nurr1 gene therapy and Nurr1 activating compounds have been tested in animal models of PD, showing their effective in protecting DAergic neurons and improving behavioral deficits [219].

5.5. NIr

NIr has been applied in clinical practice mainly for treating tissue contusion for many years. Previous preclinical studies have demonstrated that NIr could improve behavior deficits and DAergic neurons survival in parkinsonian mice [227, 228]. Remarkably, a recent primate trial has further supported the notion that NIr may be neuroprotective without severe side effects, which brings a step closer to clinical translation [229].

6. CONCLUSION

Current pharmacotherapy mainly focuses on symptomatic and neuroprotective treatment. As we can see, PD is a complex disease and its pathogenesis involves many mechanisms, such as ROS, mitochondrial dysfunction, neuroinflammation, UPS, autophagy impairment and other unknown mechanisms. Classical drug treatments with the emerging new formulations and novel drugs with novel therapeutic targets may provide better strategy for PD treatment. Many clinical trials have been carried out to evaluate the safety and effectiveness of those new therapeutic candidates, some of which have shown a good application prospect.

Although neuroprotective treatment has been controversial for decades, only few of the neuroprotective drugs have been confirmed to be effective in recent phase 2 or 3 clinical trials. We believe that a better understanding of pathogenesis and mechanisms of the disease will facilitate the discovery and development of novel drugs to control motor and non-motor symptoms and slow disease progress, and most importantly, to enhance the quality of life. In addition, non-pharmaceutical therapies of PD, such as DBS, gene therapy and cell replacement therapies, as well as other complementary management, have been demonstrated to be able to benefit PD patients to some extent. It is proposed that these new therapies may bring promise for better management of this disease.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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