Current Pharmaceutical Treatments and Alternative Therapies of Parkinson’s Disease

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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

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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  | Increase in bioavailability by approximately 100%; reduce peripheral side effects                   | [19-21]|
|                            |                                          | drug        |                                                                                                     |        |
| 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  | Improve motor symptoms and quality of life; reduce motor fluctuations (optimization of morning delay on and afternoon off periods) | [22, 32, 33]|
|                            |                                          | drug        |                                                                                                     |        |
| 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  | Increase motor and daily activities; reduce severity of basic symptoms and improve quality of life   | [39]   |
|                            | drug                                    |             |                                                                                                     |        |
| 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 multiparticals 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 acetylcholine. 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.
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 acetylcholine-esterase 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 reuptake 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 polydylain, 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 neuroprotective 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 absorptivity of 18F-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 Ca2+ 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 Ca2+ 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] |
|                                      |                                           | IIIb        | Inconclusive |                                                    | [130] |
| Granulocyte-colony stimulating factors | Anti-apoptotic, neurogenesis induction, immunity modulation | II | Inconclusive | Early-start patients respond earlier to medicine; slow disease progression compared to delayed-start group | [131] |
| Deferiprone                          | Iron chelator                             | II/III      | Completed  | Isradipine 10 mg/d was the maximal tolerable dosage and the common side effects are edema and dizziness | [132] |
|                                      |                                           | III         | Ongoing    |                                                      | [133] |
|                                      |                                           | 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] |
| Selegiline                           | MAO-B inhibitor (antioxidant/antiapoptotic) | III         | Completed  | A significant difference between early-start and delayed-start groups with rasagiline 1 mg | [144] |
| Ropinirole                           | D2/D3 receptor agonist                    | III         | Completed  | Delay the start of PD symptoms                       | [50]  |
| Pramipexole                          | D2/D3 receptor agonist                    | III         | Completed  | Slow the loss of DA neurons                          | [145] |
|                                      |                                           | IV          | Completed  | Slow the degeneration of DA neurons                  | [146] |
|                                      |                                           |             |            | 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 neurotogenic 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 UPDRS 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 test 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 rikkunshito could reduce gastrropasms in terms of shortening gastric emptying time in PD [209]. Yokuksans in 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 Nur1 is a promising therapeutic target for PD. Nur1 gene therapy and Nur1 activating compounds have been tested in animal models of PD, showing their effective in protecting DAergic neurons and improving behavioral deficits [219].

5.5. Nlr

Nlr has been applied in clinical practice mainly for treating tissue contusion for many years. Previous preclinical studies have demonstrated that Nlr could improve behavior deficits and DAergic neurons survival in parkinsonian mice [227, 228]. Remarkably, a recent primates trial has further supported the notion that Nlr 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 nonmotor symptoms and slow disease progress, and most importantly, to enhance the quality of life. In addition, nonpharmaceutical 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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REFERENCES

[1] Tarsy, D. Treatment of Parkinson disease: a 64-year-old man with motor complications of advanced Parkinson disease. JAMA, 2012, 307(21), 2305-2314. doi: 10.1001/jama.2012.4829.

[2] Gillies, G.E.; Pienaar, I.S.; Vohra, S.; Qamhawi, Z. Sex Differences in Parkinson’s Disease. Front. Neuroendocrinol, 2014, 35 (3), 370-384. doi: 10.1016/j.yfnef.2014.02.002.

[3] Fahn, S. Description of Parkinson’s Disease as a Clinical Syndrome. Ann. N. Y. Acad. Sci., 2003, 991, 1-14.

[4] Zuo, L.; Motherwell, M.S. The Impact of Reactive Oxygen Species and Genetic Mitochondrial Mutations in Parkinson’s Disease. Gene., 2013, 532(1), 18-23. doi: 10.1016/j.gene.2013.07.085.

[5] Ciechanover, A.; Kwon, Y.T. Degradation of Misfolded Proteins in Neurodegenerative Diseases: Therapeutic Targets and Strategies. Exp. Mol. Med., 2015, 47, e147. doi: 10.1038/emm.2014.117.

[6] Hirsch, E.C.; Jenner, P.; Przedborski, S. Pathogenesis of Parkinson’s Disease. Mov. Disord., 2013, 28(1), 24-30. doi: 10.1002/mds.25032.

[7] Verstraeten, A.; Theuns, J.; Van Broeckhoven, C. Progress in Parkinson’s Disease. Parkinsonism. Gene., 2013, 532(1), 18-23. doi: 10.1016/j.gene.2013.07.085.

[8] Pacione, E.; Fabbro, M.; Causin, M.; Nyholm, D. Continuous Drug Delivery in Parkinson’s Disease: A Randomised, Controlled, Double-Blind Trial. Lancet Neurol., 2013, 12(4), 346-356. doi: 10.1016/S1474-4422(13)70025-5.

[9] Verhagen M.L.; Stover, N.; Chen, C.; Cowles, V.E.; Sweeney, M. Gastroretentive Carbidopa/levodopa, DM-1992, for the Treatment of Advanced Parkinson’s Disease. Mov. Disord. 2015, 30(9), 1222-1228. doi: 10.1002/mds.26219

[10] Science et al. Parkinson’s Disease: A Randomised, Controlled, Double-Blind, Double-Dummy Study. Lancet Neurol., 2014, 13(2), 141-149. http://dx.doi.org/10.1016/S1474-4422(13)70293-X

[11] Nagy, H.; Takats, A.; Tóth, A.; Bereczki, D.; Klivényi, P.; Dézsi, L.; Bíbó, G.; Vécsei, L.; Kovács, N.; Aschermann, Z.; Komoly, S.; Varramai, L.; Zemplényi, G.; Valkovic, A. Experience with levodopa/carbidopa intestinal gel in the treatment of advanced Parkinson’s disease in Hungary. J. of Neuroggy Sz., 2014, 67(11-12), 385-9.

[12] Freed M.I.; Batycke R.; Merica E. Safety, tolerability and levodopa pharmacokinetics following inhale administration of CTV-301, a levodopa dry powder aerosol, in healthy, adult subjects. Mov. Disord. 2013, 28, S154-S154.

[13] Lee, Y.H.; Kim, K.H.; Yoon, I.K.; Lee, I.K.; Rhie, J.Y.; Ghim, H.; Kwak, H.S. Pharmacokinetic Evaluation of Formulated Levodopa. J. of Neuroggy Sz., 2014, 67(11-12), 385-9.

[14] Xie, C.; Wang, W.W.; Zhang, S.; Yuan, M.C.; Chiu, Y.J.; Gan, J.; Song, L.; Tian, Y. Parkinson’s Disease Experiencing Motor Fluctuations. With Levodopa Methylester (Melevodopa) in Patients With Parkinson Disease. Mov. Disord., 2014, 29(2), 1222-1228. doi: 10.1002/mds.26219

[15] Quinn, N.; Marsden, C.D.; Parkes, J.D. Complicated response fluctuations in Parkinson’s disease: response to intravenous infusion of levodopa. Lancet, 1982, 2(8295), 412-415.

[16] Olanov, C.W.; Kieburtz, K.; Odin, P.; Espay, A.J.; Standaert, D.G.; Fernandez, H.H.; Vanagunas, A.; Othman, A.L.; Widekl, K.L.; Roberson, W.Z.; Pritchett, Y.; Chhatram, K.; Benesh, J.; Lenz, R.; Antonini, A. Continuous Intrajejunal Infusion of Levodopa-Carbidopa Intestinal Gel for Patients with Advanced Parkinson’s Disease: A Randomised, Controlled, Double-Blind, Double-Dummy Study. Lancet Neurol., 2014, 13(2), 141-149. http://dx.doi.org/10.1016/S1474-4422(13)70293-X

[17] Dibó, L.; Bíbó, G.; Vécsei, L.; Kovács, N.; Aschermann, Z.; Komoly, S.; Varramai, L.; Zemplényi, G.; Valkovic, A. Experience with levodopa/carbidopa intestinal gel in the treatment of advanced Parkinson’s disease in Hungary. J. of Neuroggy Sz., 2014, 67(11-12), 385-9.

[18] Freed M.I.; Batycke R.; Mircia E. Safety, tolerability and levodopa pharmacokinetics following inhalation administration of CTV-301, a levodopa dry powder aerosol, in healthy, adult subjects. Mov. Disord. 2013, 28, S154-S154.

[19] Lee, Y.H.; Kim, K.H.; Yoon, I.K.; Lee, I.K.; Rhie, J.Y.; Ghim, H.; Kwak, H.S. Pharmacokinetic Evaluation of Formulated Levodopa. J. of Neuroggy Sz., 2014, 67(11-12), 385-9.

[20] Mancini, F.; Comi, C.; Oggioni, G.D.; Pacchetti, C.; Candrellara, D.; Coletti Moja, M.; Riboldazzi, G.; Tunesi, S.; Dal Fante, M.; Manfredi, L.; Lacerenza, M.; Cantello, R.; Antonini, A. Prevalence and Features of Peripheral Neuropathy in Parkinson’s Disease Patients under Different Therapeutic Regimens. Parkinsonism Relat. Disord., 2014, 20(1), 27-31. http://dx.doi.org/10.1016/j.parkreldis.2013.09.007

[21] Kovacs, N.; Aschermann, Z.; Acs, P.; Bosnyak, E.; Deli, G.; Janszky, J.; Komoly, S. The Impact of Levodopa-Carbidopa Intestinal Gel on Health-Related Quality of Life in Parkinson’s Disease. J. of Neuroggy Sz., 2014, 67(7-8), 245-250.

[22] Stocchi, F.; Barbato, L.; Bramante, L.; Bonamartini, A.; Ruggieri, S. The clinical efficacy of a single afternoon dose of levodopa methyl ester: a double-blind cross-over study versus placebo. Br. J. of Neuroggy Sz., 2014, 67(7-8), 245-250.

[23] Zangaglia, R.; Stocchi, F.; Scarinetta, M.; Antonini, A.; Mancini, F.; Guidi, M.; Martignoni, E.; Pacchetti, C. Clinical Experiences With Levodopa Methylster (Melevodopa) in Patients With Parkinson Disease Experiencing Motor Fluctuations. Clin. Neuropharmacol., 2010, 33(2), 61-66. http://dx.doi.org/10.1097/WNF.0b013e3181c5e60c

[24] Cahka, R.; Lyons, K.E.; Hauser, R.A.; Fahn, S.; Jankovic, J.; Pourcher, E.; Hsu, A.; O’Connell, M.; Kell, S.; Gupta, S. Randomized Trial of IPX066, Carbidopa/levodopa Extended Pharmacokinetics of Levodopa/Carbidopa Microtablets Versus Levodopa/Benserazide and Levodopa/Carbidopa in Healthy Volunteers. Clin. Neuropharmacol., 2012, 35(3), 111-117. doi: 10.1097/WNF.0b013e31825645fd.
Drug Treatment and Alternative Therapy for PD

Current Neuropharmacology. 2016. Vol. 14. No. 4 349

Pålphagen, S.; Heinonen, E.; Hägglund, J.; Kaugersaar, T.; Mäki-Ikola, O.; Palm, R. Selegeline Slows the Progression of the Symptoms of Parkinson’s Disease. Neurology. 2006, 66(8), 1200-1206. http://dx.doi.org/10.1212/01.wnl.0000240074.46190.54

Müller, T.; Hoffmann, J.A.; Dimpfel, W.; Oehlerwien, C. Switch from Selegeline to Rasagiline Is Beneficial in Patients with Parkinson’s Disease. J. Neural Transm. 2013, 120 (5), 761-765. http://dx.doi.org/10.1007/s00702-012-0927-3

Deeks, E. D. Saingafmine: First Global Approval. Drugs, 2015, 75(6), 705-711. http://dx.doi.org/10.1007/s40265-015-0389-7

Borgohain, R.; Szasz, J.; Stanzione, P.; Meshram, C.; Bhatt, M.H.; Chirilunea, D.; Stocchi, F.; Lucini, V.; Gianuli, R.; Forrest, E.; Pe, P.; Anand, R. Two-Year, Randomized, Controlled Study of Saingafmine as Add-on to Levodopa in Mid to Late Parkinson’s Disease. Mov. Disord. 2014, 29(10), 1273-1280.

Borgohain, R.; Szasz, J.; Stanzione, P.; Meshram, C.; Bhatt, M.; Chirilunea, D.; Stocchi, F.; Lucini, V.; Gianuli, R.; Forrest, E.; Pe, P.; Anand, R. Randomized Trial of Saingafmine Add-on to Levodopa in Parkinson’s Disease with Motor Fluctuations. Mov. Disord., 2014, 29(2), 229-237. http://dx.doi.org/10.1002/mds.25751

Mahmood, I. Clinical Pharmacokinetics and Pharmacodynamics of Selegeline. An Update. Clin. Pharmacokinet., 1997, 33(2), 91-102. http://dx.doi.org/10.2165/00003188-19973302-00002

Tabi, T.; Szökö, E.; Vecsei, L.; Magyar, K. The Pharmacokinetic Elevation of Levodopa Dosage During Saingadopa. Sustained-Release Carbidopa-Levodopa (Sinemet(R)), Carbidopa-Levodopa-Entacapone (Stalevo(R)). J. Clin. Pharmacol., 2015. [Epub ahead of print], http://dx.doi.org/10.1002/jcph.514

LeWitt, P.A.; Huff, F.J.; Hauser, R.A.; Chen, D.; Lissin, D.; Zomorodi, K.; Cundy, K.C. Double-Blind Study of the Actively Transported Levodopa Prodrug XPD2179 in Parkinson’s Disease. Mov. Disord., 2014, 29(1), 75-82. doi:10.1002/mds.25742.

Hinson, V.K.; Goetz, C.G.; Leurgans, S.; Fan, W.; Nguyen, T.; Hsu, A. Reducing Dosing Frequency of Carbidopa-Levodopa. Clin. Neuropharmacol., 2009, 32(4), 189-192. http://dx.doi.org/10.1097/WNF.0b013e31812a7fae

Schrag, A. Entacapone in the Treatment of Parkinson’s Disease. Lancet Neurol., 2005, 4, 366-370. http://dx.doi.org/10.1016/S1474-4221(05)00998-3

Liasichchenko, E.A.; Skripkina, N.A.; Levin, O.S. Influence of Levodopa, Stalevo on Dyskinesia in Parkinson’s Disease: STRIDE-PD Study. Zh. Nevrol. Psikhiatr. Im. S. S. Korotkova, 2013, 113(7 Pt 2), 62-68.

Alishammar, T.M.; AlMutairi, E.N. Use of an Entacapone-Containing Drug Combination and Risk of Death: Analysis of the FDA AERS (FAERS) Database. Saudi Pharm. J., 2015, 23(1), 28-32. http://dx.doi.org/10.1016/j.jsps.2014.04.005

Ferreira, J.J.; Rascol, O.; Poewe, W.; Sampaio, C.; Rocha, J.F.; Nunes, T.; Almeida, L.; Soares-da-Silva, P. A Double-Blind, Randomized, Placebo and Active-Controlled Study of Ncobcapone for the Treatment of Motor Fluctuations in Parkinson’s Disease. CNS Neurosci. Ther., 2010, 16(6), 337-347. http://dx.doi.org/10.1111/j.1755-5949.2010.00145.x

Ferreira, J.J.; Almeida, L.; Cunha, L.; Tcmeanou, M.; Rosa, M.M.; Januario, C.; Mitu, C.E.; Coelho, M.; Correia-Guedes, L.; Morgadinho, A.; Nunes, T.; Wright, L.C.; Falcao, A.; Sampaio, C.; Soares-da-Silva, P. Effects of Ncobcapone on Levodopa Pharmacokinetics, Catechol-O-Methyltransferase Activity, and Motor Fluctuations in Patients with Parkinson Disease. Clin. Neuropharmacol., 2008, 31(1), 2-18. http://dx.doi.org/10.1097/wnf.0b013e3180645c6b

Ferreira, J.J.; Rocha, J.F.; Falcao, A.; Santos, A.; Pinto, R.; Nunes, T.; Soares-da-Silva, P. Effects of Ncobcapone on Levodopa Pharmacokinetics, Catechol- O-Methyltransferase Activity and Motor Fluctuations in Patients with Parkinson’s Disease. Eur. J. Neurol., 2015, 22 (5), 815-856. http://dx.doi.org/10.1111/ene.12666

Bonifacio, M.J.; Torrao, L.; Loureiro, A.I.; Palma, P.N.; Wright, L.C.; Soares-da-Silva, P. Pharmacological Profile of Opicapone, a Third-Generation Nitrocatechol Catechol- O-Methyl Transferase Inhibitor, in the Rat. Br. J. Pharmacol., 2015, 172(7), 1739-1752. http://dx.doi.org/10.1111/bph.13020

Tetrad, J.W.; Langston, J.W. The effect of deprenyl (selegiline) on the natural history of Parkinson’s disease. Science, 1989, 245(4917), 519-22. http://dx.doi.org/10.1126/science.2502843

[35] Mao, Z.; Hsu, A.; Gupta, S.; Modi, N.B. Population Pharmacodynamics of IPX066: An Oral Extended-Release Capsule Formulation of Carbidopa-Levodopa, and Immediate-Release Carbidopa-Levodopa in Patients With Advanced Parkinson’s Disease. J. Clin. Pharmacol., 2013, 53(5), 523-531. http://dx.doi.org/10.1002/jcph.63

[36] LeWitt, P.; F.H.; Giladi, N. Accordion pill carbidopa/levodopa for improved symptomatic treatment of advanced Parkinson’s disease. Mov. Disord., 2012, 27, S1-S23.

[37] Giladi, N.; Cano, Y.; Gurevich, T.; Djalldetti, R.; Cohen, Y.; Yacoobi-Zaevi, O.; Oren, S. Pharmacokinetics and safety of ND0612L (levodopa/carbidopa for subcutaneous infusion): Results from a phase II study in moderate to severe Parkinson’s disease. Age (years)., 2015, 63(74), 64-65.

[38] Kuoppamaki, M.; Trenkwalder, C.; Vaheristo, M.; Moshunje, A.; Aho, V.; Ellemen, J. Phase II proof of concept study to compare a novel levodopa product ODM-101 to levodopa/carbidopa/entacapone in Parkinson’s disease patients with response fluctuations (S23.005). Neurology, 2013, 89(S23), 5.

[39] Hsu, A.; Yao, H.M.; Gupta, S.; Modi, N.B. Comparison of the Pharmacokinetics of An Oral Extended-Release Capsule Formulation of Carbidopa-Levodopa (IPX066), with Immediate-Release Carbidopa-Levodopa (Sinemet(R)). J. Neuro. Sci., 2012, 322, 2245(4917), 519-22. http://dx.doi.org/10.1111/j.1528-1147.2012.03740.x

[40] Tetrud, J.W.; Langston, J.W. The effect of deprenyl (selegiline) on the natural history of Parkinson’s disease. Science, 1989, 245(4917), 519-22. http://dx.doi.org/10.1126/science.2502843

[41] Grill, E.; Rinne, J.; van der Flier, W.M.; Siesjö, B.K.; Brundin, P. Therapeutic Heat Induced Thrombosis in the Rat. Br. J. Pharmacol., 2013, 172, 1739-1752. http://dx.doi.org/10.1111/bph.13020

[42] Zhu, C.Q.; Lou, J.H.; Zhang, Y.P.; Zhong, L.; Chen, Y.L.; Lu, F. J.; Peng, G.G. Long Acting Versus Standard Non Ergot Dopamine Agonists in Parkinson’s Disease: A Meta-Analysis of Randomized Controlled Trials. CNS Neurosci. Ther., 2014, 20(4), 368-376. http://dx.doi.org/10.1111/cns.12239
Tremor: Possible Role of M4 Receptors.

Betz, A.J.; McLaughlin, P.J.; Burgos, M.; Weber, S.M.; Salamone

Serotonin 5-

S.; Ali, M.; Baboota, S.; Sahni, J.K.; Kumari, B.;

Mizuno, Y.; Kondo, T.; Hasegawa, K.; Murata, M.;

Elshoff, J.P.; Cawello, W.; Andreas, J.O.; Mathy, F.X.; Braun, M.

An Update on Pharmacological, Pharmacokinetic Properties and Drug-Drug Interactions of Rotigotine Transdermal System in Advanced Parkinson's Disease and Restless Legs Syndrome. Drugs, 2015, 75(5), 487-501.

Nomoto, M.; Mizuno, Y.; Kondo, T.; Hasegawa, K.; Murata, M.; Takeuchi, M.; Ikeda, J.; Tomida, T.; Hattori, N. Transdermal Rotigotine in Advanced Parkinson's Disease: A Randomized, Double-Blind, Placebo-Controlled Trial. J. Neurol. 2014, 261(10), 1887-1893.

Grosset, K.A.; Malek, N.; Morgan, F.; Grosset, D.G. Inhaled Apomorphine in Patients with "off-on" Fluctuations: A Randomized, Double-Blind, Placebo-Controlled, Clinical and Home Based, Parallel-Group Study. J. Parkinsons Dis., 2013, 3(1), 31-37.

Yamada, K.; Miyachi, N.; Kanda, T. Subcutaneous Apomorphine Injection: Rescue Management of Motor Fluctuations Associated with Levodopa-Therapy: Nikhon Yakurigoto Zasshi., 2013, 141(2), 44-51. http://dx.doi.org/10.1254/fpj.141.44

Trenkwalder, C.; Boeck, S.; Ceballos-Baumann, A.; Dressler, D.; Eggert, K.; Gasser, T.; Honig, H.; Muller, T.; Reichmann, H.; Sieb, J.P.; Storch, A.; Poeze, W. Intermittierende Apomorphin-Injektionen Als Rescue-Therapie Beim Fortgeschrittenen M. Parkinson. Nervenarzt., 2007, 78(4), 475-479. http://dx.doi.org/10.1007/s00115-007-2391-0

Long-Term Safety Study of KW-6500 in Patients With Parkinson's Disease. https://www.clinicaltrials.gov/ct2/show/NCT00955318.

Long-Term Safety Study of Open-label Pramipexole Extended Release (ER) in Patients With Early Parkinson's Disease (PD). https://www.clinicaltrials.gov/ct2/show/NCT00601523.

A Study to Examine APL-130277 in Patients With Parkinson's Disease. https://www.clinicaltrials.gov/ct2/show/NCT02228590.

Efficacy and Safety Study of Aplindore in Patients With Early Parkinson Disease. https://www.clinicaltrials.gov/ct2/show/NCT0089302.

Rascol, O.; Azulay, J.P.; Blin, O.; Bonnet, A.M.; Brefel-Courbon, C.; Cesaro, P.; Damier, P.; Dehilly, B.; Durif, F.; Galitzky, M.; Grouin, J.M.; Pennafort, S.; Villafane, G.; Yaici, S.; Agid, Y. Ondansetron and Biperiden: Two New and Potent Dementia Drugs for Alzheimer's Disease. Neurology, 2010, 75(12), e15298. http://dx.doi.org/10.1016/j.ncl.2010.02.098

Phase II Multicentre Study Investigating of VR040 in Parkinson's Disease (VR040/2003). http://www.clinicaltrials.gov/ct2/show/NCT01693081

Jafarieh, O.; Md, S.; Ali, M.; Baboota, S.; Sahni, J.K.; Kumari, B.; Bhatnagar, A.; Ali, J. Design, Characterization, and Evaluation of Intranasal Delivery of Ropinirole-Loaded Macrodextrine Nanoparticles for Brain Targeting. Drug Dev. Ind. Pharm., 2014, 40(10), 1-8.

Zhao, R.; Lu, W.; Fang, X.; Guo, L.; Yang, Z.; Ye, N.; Zhao, J.; Liu, Z.; Jia, J.; Zheng, L.; Zhao, B.; Zhang, A.; Zhen, X. (6αR)-11-Amino-N-Prolyl-Norapomorphine, a New Dopamine D2 and Serotonin 5-HT1A Dual Agonist, Elicits Potent Antiparkinsonian Action and Attenuates Levodopa-Induced Dyskinesia in a 6-OHDA-Lesioned Rat Model of Parkinson's Disease. Pharmacol. Biochem. Behav., 2014, 124, 204-210. http://dx.doi.org/10.1016/j.pbb.2014.06.011

Betz, A.J.; McLaughlin, P.J.; Burgos, M.; Weber, S.M.; Salamone, J.D. The Muscarinic Receptor Antagonist Tropicamide Suppresses Tremulous Jaw Movements in a Rodent Model of Parkinsonian Tremor: Possible Role of M4 Receptors. Psychopharmacology (Berl.), 2007, 194(3), 347-359. http://dx.doi.org/10.1007/s00213-007-0844-6

Koller, W.C. Pharmacologic treatment of parkinsonian tremor. Arch NeuroL., 1986, 43(2), 126-127. http://dx.doi.org/10.1010/archneur.1986.005200200099

Wawruch, M.; Macugova, A.; Kostkova, L.; Luha, J.; Dukat, A.; Murin, J.; Droba, N.; Wilton, L.; Kuzelova, M. The Use of Medications with Anticholinergic Properties and Risk Factors for Their Use in Hospitalised Elderly Patients. Pharmacoepidemiol. Drug Saf., 2012, 21(2), 170-176. http://dx.doi.org/10.1002/pds.2169

Lodi, F.; Dell'Aquila, G.; Collamati, A.; Martone, A.M.; Zuliani, G.; Gasperini, B.; Eusebi, P.; Lattanzio, F.; Cherubini, A. Anticholinergic Drug Use and Negative Outcomes Among the Frail Elderly Population Living in a Nursing Home. J. Am. Med. Dir. Assoc., 2014, 15(11), 825-829. http://dx.doi.org/10.1016/j.jamda.2014.08.002

Perez-Lloret, S.; Negre-Pages, L.; Damier, P.; Delval, A.; Derkinderen, P.; Destée, A.; Meissner, W.G.; Schelosky, L.; Tison, F.; Rascol, O. Prevalence, Determinants, and Effect on Quality of Life of Freezing of Gait in Parkinson Disease. JAMA NeuroL., 2014, 71(7), 884. http://dx.doi.org/10.1001/jamaneurol.2014.753

Sakakibara, R. Cognitive Adverse Effects of Anticholinergic Medication for Overactive Bladder in PD/DLB. Rusko Sanki, 2014, 3(11), 1389-1392. http://dx.doi.org/10.5692/clinicalneurologia.m.13389

Hubsher, G.; Haider, M.; Okun, M.S. Amantadine: The Journey From Fighting Flu to Treating Parkinson Disease. Neurology, 2012, 78(14), 1096-1099. http://dx.doi.org/10.1212/WNL.0b013e3182315e08fd

Lee, J.Y.; Oh, S.; Kim, J.M.; Kim, J.S.; Oh, E.; Kim, H.T.; Jeon, B.S.; Cho, J.W. Intravenous Amantadine on Freezing of Gait in Parkinson’s Disease: A Randomized Controlled Trial. J. Neurol., 2013, 260(12), 3030-3038. http://dx.doi.org/10.1007/s00415-013-7108-7

Pereira Da Silva-Junior, F.; Braga-Neto, P.; Souli Monte, F.; Meireles Sales De Bruin, V. Amantadine Reduces the Duration of Levodopa-Induced Dyskinesia: A Randomized, Double-Blind, Placebo-Controlled Study. Park. Relat. Disord., 2005, 11(7), 449-452. http://dx.doi.org/10.1016/j.parkreldis.2005.05.008

Sawada, H.; Oeda, T.; Kuno, S.; Nomoto, M.; Yamamoto, K.; Yamamoto, M.; Hisanaka, K.; Kawamura, T. Amantadine for Dyskinesias in Parkinson’s Disease: A Randomized Controlled Trial. Park. Relat. Disord. 2013, 19(3), 316-319. http://dx.doi.org/10.1016/j.parkreldis.2012.11.005

Cera, N.; Bifolchetti, S.; Martinotti, G.; Gambi, F.; Sepede, G.; Thomas, A.; Di Giannantonio, M.; Onofri, M. Amantadine and cognitive flexibility: decision making in Parkinson's patients with severe pathological gambling and other impulse control disorders. Neuropsychiatr. Dis. Treat., 2014, 10, 1093-1101. http://dx.doi.org/10.2147/NDT.S54423

Ory Magne, F.; Corvol, J. C.; Azulay, J.P.; Bonnet, A.M.; Brefel Courbon, C.; Damier, P.; Delapaina, E.; Destée, A.; Durif, F.; Galitzky, M.; Lebouvier, T.; Meissner, W.; Thalamas, C.; Tison, F.; Sails, A.; Sommet, A.; Viallet, F.; Vidalhiet, M.; Rascol, O. Withdrawing Amantadine in Dyskinetic Patients with Parkinson Disease: The AMANDYSK Study. Neurology, 2014, 82(4), 300-307. http://dx.doi.org/10.1212/WNL.0000000000000050

Thomas, A.; Iacono, D.; Luciano, A.L.; Armellino, K.; Di Iorio, A.; Onofri, M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. J. Neurol. Neurosurg. Psychiatry, 2004, 75(1), 141-3.
Influence of the Nonergot Dopamine Agonist Piribedil on Vigilance

Eggert, K.; Öhlwein, C.; Kassubek, J.; Wolz, M.; Kupsch, A.; Blind, Pilot Evaluation of Intravenous Acetylcysteine for Neuroprotection in Parkinson’s Disease. Mov. Disord., 2015, 30(8), 1027-1033. doi:10.1002/mds.26310

Zibetti, M.; Rizzone, M.; Merola, A.; Angrisano, S.; Rizzi, L.; Montanaro, E.; Cicolin, A.; Lopiano, L. Sleep Improvement with Levodopa/carbidopa Intestinal Gel Infusion in Parkinson Disease. Acta Neurol. Scand., 2013, 127(5), e28-e32. http://dx.doi.org/10.1111/ane.12075

Kulsa, T.; Fedorova, N. V.; Popovkina, O. A. Nocturnal Motor Symptoms of Parkinson’s Disease and Their Treatment with the Three-Component Drug Levodopa/carbidopa/entacapone. Zhurnal Neirov. i Psihiatr. Im. S.S. Korsakova., 2011, 119(9), 45-50.

Rios Romenets, S.; Creti, L.; Fichten, C.; Bailes, S.; Libman, E.; Pelletier, A.; Postuma, R.B. Dopamine and Cognitive Behavioural Therapy for Insomnia in Patients with Parkinson’s Disease - A Randomized Study. Parkinsonism Relat. Disord., 2013, 19(7), 670-675. http://dx.doi.org/10.1016/j.parkreldis.2013.03.003

Di Giacopo, R.; Fassano, A.; Quaranta, D.; Marca, G.; Della; Bove, F.; Bentivoglio, A.R. Rivastigmine as Alternative Treatment for Refractory REM Behavior Disorder in Parkinson’s Disease. Mov. Disord., 2012, 27(4), 559-561. http://dx.doi.org/10.1002/mds.24909

Ricciardi, L.; De Nigris, F.; Specchia, A.; Fasano, A. Homotaurine in Parkinson’s Disease. Neuro. Sci., 2015, 36(9), 1581-1587. http://dx.doi.org/10.1007/s10072-015-2201-6

Troeung, L.; Egan, S.J.; Gasson, N. A. Meta-Analysis of Randomised Placebo-Controlled Treatment Trials for Depression and Anxiety in Parkinson’s Disease. PLoS One, 2013, 8(11), e80554. http://dx.doi.org/10.1371/journal.pone.0080554

Liu, J.; Dong, J.; Wang, L.; Su, Y.; Yan, P.; Sun, S. Comparative Efficacy and Acceptability of Antidepressants in Parkinson’s Disease: A Network Meta-Analysis. PLoS One, 2013, 8(10), e76651. http://dx.doi.org/10.1371/journal.pone.0076651

Smith, K. M.; Eyal, E.; Weintraub, D. Combined Rasagiline and Antidepressant Use in Parkinson Disease in the ADAGIO Study. JAMA Neuro., 2015, 72(1), 88. http://dx.doi.org/10.1001/jamaneuro.2014.2472

Fernie, B.A.; Kollmann, J.; Brown, R.G. Cognitive Behavioural Interventions for Depression in Chronic Neurological Conditions: A Systematic Review. J. Psychosom. Res., 2015, 78(5), 411-419. http://dx.doi.org/10.1016/j.jpsychores.2015.02.012

Sugapura, A.; Kühn, C.; Mangel, C.W.; Green, J.; Bezard, E. Slowing of Neurodegeneration in Parkinson’s Disease and Huntington’s Disease: Future Therapeutic Perspectives. Lancet., 2014, 384(9942), 545-555. http://dx.doi.org/10.1016/S0140-6736(14)60102-2

Filogarano, R.; Beltramini, M. http://dx.doi.org/10.1002/mds.22401

Chen, Y.; Zhang, D.; Cai, H.; Wang, B.; Gong, S.; Wang, C.; Zhang, M.; Wang, G.; Cai, H.; Liao, F.; Xu, J. Anti-Oxidant Polydatin (piced) Protects against Substantia Nigral Motor Degeneration in Multiple Rodent Models of Parkinson’s Disease. Mov. Neurolog., 2015, 10(4), 1. http://dx.doi.org/10.1016/j.mnrx.2015.01.008

Holmøy, M.J.; Terpstra, M.; Coles, L.D.; Mishra, U.; Ahlskog, J.E.; Aarsland, D. The CamPaIGN Study of Acetylcholinesterase Inhibitors and Memantine in Cognitive Impairment in Parkinson’s Disease, Parkinson’s Disease Dementia, and Dementia with Lewy Bodies: Systematic Review with Meta-Analysis and Trial Sequential Analysis. J. Neurol. Neurosurg. Psychiatry., 2015, 86(2), 135-143. http://dx.doi.org/10.1136/jnnp-2014-307659

Schapira, A.H.V; Olanow, C.W.; Greenamyre, J.T.; Bezard, E. Slowing of Neurodegeneration in Parkinson’s Disease and Huntington’s Disease: Future Therapeutic Perspectives. Lancet., 2014, 384(9942), 545-555. http://dx.doi.org/10.1016/S0140-6736(14)60102-2

Bubacco, L.; Bisaglia, M. A. Nocturnal Motor Symptoms of Parkinson’s Disease. J. Neurol. Neurosurg. Psychiatry., 2015, 86(2), 135-143. http://dx.doi.org/10.1136/jnnp-2014-307659

Lutfi, S.; Kassubek, J.; Storch, A.; Reichmann, H. Sleep Disorders in Parkinson’s Disease. J. Parkinsons. Dis., 2014, 4(2), 211-221.

Kerrigan, D.J.; Overduin, R.; Stewart, R.; Marzolf, L.; Waller, L. Sleep in Patients with Parkinson’s Disease and Excessive Daytime Sleepiness. http://dx.doi.org/10.1097/WNF.0b013e31829ae713

Zibetti, M.; Rizzone, M.; Merola, A.; Angrisano, S.; Rizzi, L.; Montanaro, E.; Cicolin, A.; Lopiano, L. Sleep Improvement with Levodopa/carbidopa Intestinal Gel Infusion in Parkinson Disease. Acta Neurol. Scand., 2013, 127(5), e28-e32. http://dx.doi.org/10.1111/ane.12075

Rios Romenets, S.; Creti, L.; Fichten, C.; Bailes, S.; Libman, E.; Pelletier, A.; Postuma, R.B. Dopamine and Cognitive Behavioural Therapy for Insomnia in Patients with Parkinson’s Disease - A Randomized Study. Parkinsonism Relat. Disord., 2013, 19(7), 670-675. http://dx.doi.org/10.1016/j.parkreldis.2013.03.003

Di Giacopo, R.; Fassano, A.; Quaranta, D.; Marca, G.; Della; Bove, F.; Bentivoglio, A.R. Rivastigmine as Alternative Treatment for Refractory REM Behavior Disorder in Parkinson’s Disease. Mov. Disord., 2012, 27(4), 559-561. http://dx.doi.org/10.1002/mds.24909

Ricciardi, L.; De Nigris, F.; Specchia, A.; Fasano, A. Homotaurine in Parkinson’s Disease. Neuro. Sci., 2015, 36(9), 1581-1587. http://dx.doi.org/10.1007/s10072-015-2201-6
Parkinson’s Disease (PROUD): A Phase II Safety, Tolerability, and Dose Selection Study of Ipadipine as a Potential Disease-Modifying Intervention in Early Parkinson’s Disease (STEADY-PD). Mov. Disord., 2013, 28(13), 1823-1831. http://dx.doi.org/10.1002/mds.25639

Efficacy of Ipadipine in Early Parkinson Disease. https://clinicaltrials.gov/ct2/show/NCT02168842.

Storch, A.; Jost, W.H.; Viergege, P.; Spiegel, J.; Greulich, W.; Durner, J.; Müller, T.; Kupsch, A.; Henninger, H.; Oertel, W.H.; Fuchs, G.; Kuhn, W.; Niklowitz, P.; Koch, R.; Herting, B.; Reichmann, H. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q10 in Parkinson disease. Arch. Neurol., 2007, 64(9), 938-944. http://dx.doi.org/10.1001/archneur.64.9.960005

Jang, W.; Park, J.; Shun, K.J.; Kim, J.S.; Kim, J.Y.; Youn, J.; Cho, J.H.; Oh, E.; Ahn, J.Y.; Oh, K.W.; Kim, H.T. Safety and Efficiency of Recombinant Human Erythropoietin Treatment of Non-Motor Symptoms in Parkinson’s Disease. J. Neurol. Sci., 2014, 337(1-2), 47-54. http://dx.doi.org/10.1016/j.jns.2013.11.015

Pedrosi, I.; Bringas, M.L.; Aguair, A.; Morales, L.; Alvarez, M.; Valdes, P. A.; Alvarez, L. Use of Cuban Recombinant Human Erythropoietin in Parkinson Disease Treatment. MEDICC Rev., 2012, 14(1), 11-17.

Ravina, B. A Randomized, Double-Blind, Futility Clinical Trial of Creatine and Nicotinamide in Early Parkinson Disease. Neurology, 2006, 66(5), 664-671. http://dx.doi.org/10.1212/01.wnl.0000201252.57661.e1

A Pilot Clinical Trial of Creatine and Nicotinamide in Early Parkinson Disease. Clin. Neuropharmacol., 2008, 31(3), 141-150. http://dx.doi.org/10.1097/WNF.0b01318131432f22

Folytine, T.; Aviles-Olmos, I. Exenatide as a Potential Treatment for Patients with Parkinson’s Disease: First Steps into the Clinic. Alzheimer’s Dementia, 2014, 10(1), S38-S46. http://dx.doi.org/10.1016/j.jalz.2013.12.005

Trial of Exenatide for Parkinson's Disease (EXENATIDE-PD). https://clinicaltrials.gov/ct2/show/NCT01971242.

A Randomized Clinical Trial of Coenzyme Q10 and GPI-1485 in Early Parkinson Disease. Neurology, 2007, 68(1), 20-28. http://dx.doi.org/10.1212/01.wnl.0000250355.28474.8e

Olman, C.W.; Rascol, O.; Hauser, R.; Feigin, P.D.; Jankovic, J.; Langston, W.; Melamed, E.; Stocke, F.; Tolosa, E. A Double-Blind, Delayed-Study Trial of Rasagiline in Parkinson’s Disease. N. Engl. J. Med., 2009, 361(13), 1268-1278. http://dx.doi.org/10.1056/NEJMoa0809335

Rascol, O.; Fitzner-Attas, C.J.; Hauser, R.; Jankovic, J.; Lang, A.; Langston, J.W.; Melamed, E.; Poewe, W.; Stocchi, F.; Tolosa, E.; Eyal, E.; Weiss, Y.M.; Olman, C.W. A Double-Blind, Delayed Start Trial of Rasagiline in Parkinson’s Disease (the ADAGIO Study): Prespecified and Post-Hoc Analyses of the Need for Additional Therapies, Changes in UPDRS Scores, and Non-Motor Outcomes. Lancet Neurol., 2011, 10(5), 415-423. http://dx.doi.org/10.1016/S1474-4422(11)70073-4

Whone, A.L.; Watts, R.L.; Stoessl, A.J.; Davis, M.; Reske, S.; Nahmias, C.; Lang, A.E.; Rascol, O.; Ribeiro, M.J.; Remy, P.; Poewe, W.H.; Hauser, R.A.; Brooks, D.J. Slower Progression of Parkinson’s Disease with Ropinirole versus Levodopa: The REAL-PEt Study. Ann. Neurol., 2003, 53(1), 93-101. http://dx.doi.org/10.1002/ana.10609

Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA, 2004, 291(3), 1653-61. http://dx.doi.org/10.1001/jama.287.13.1653

Schapira, A.H.; McDermott, M.P.; Barone, P.; Comella, C.L.; Albrecht, S.; Hsu, H.H.; Massey, D.H.; Mizuno, Y.; Poewe, W.; Rascol, O.; Marek, K. Pramipexole in Patients with Early Parkinson’s Disease (PROUD): A Randomised Delayed-Start Trial.
Iwamuro, H.; Lefaucheur, J. P.; Thiriez, C.; Fenelon, G.; Lucas, C.; Mitrofanis, J.; Benabid, A.L. Survival of Midbrain Dopaminergic Neurons in Advanced Parkinson’s Disease: From the Advanced Phase towards the Late Stage of the Disease? Parkisonism Relat. Disord., 2014, 20(4), 376-381. http://dx.doi.org/10.1016/j.parkreldis.2014.01.012

Zarrini, M.G.; Pasano, A.; Daniele, A.; Zibetti, M.; Merola, A.; Rizzi, L.; Piano, C.; Piccininii, C.; Romito, L.M.; Lopiano, L.; Albani, A. Long-Term Outcome of Subthalamic Nucleus DBS in Parkinson’s Disease: From the Advanced Phase towards the Late Stage of the Disease? Parkisonism Relat. Disord., 2011, 17(4), 1290. http://dx.doi.org/10.1016/j.parkreldis.2011.05.001

LeWitt, P.A.; Rezaei, A.R.; Leehey, M.A.; Ojemann, S.G.; Flaherty, A.W.; Eskandar, E.N.; Kostyk, S.K.; Thomas, K.; Sarkar, A.; Siddiqui, M.S.; Tatter, S.B.; Schwab, J.M.; Poston, K.L.; Hendemer, J.M.; Kurlan, R.M.; Richardson, C.H.; Van Meter, L.; Lupon, C.V.; Dumont, J.M.; Kaplitt, M.G.; Feigina, A. AAV2-GAD Gene Therapy for Advanced Parkinson’s Disease: A Double-Blind, Sham-Surgery Controlled, Randomised Trial. Lancet Neurol., 2011, 10(4), 309-319. http://dx.doi.org/10.1016/S1474-4422(11)70039-4

Bartus, R.T.; Baumann, T.L.; Siffert, J.; Herzog, C.D.; Alterman, R.; Boullis, N.; Turner, D.A.; Stacy, M.; Lang, A.E.; Lozano, A.M.; Olano, C.W. Safety/feasibility of Targeting the Substantia Nigra with AAV2-Neurintin in Parkinson Patients. Neurology, 2013, 80(18), 1698-1701. http://dx.doi.org/10.1212/WNL.0b013e3182904faa

Mittermeyer, G.; Christine, C.W.; Rosenbluth, K.H.; Baker, S.L.; Starr, P.; Larson, P.; Kaplan, P.L.; Forsayeth, J.; Aminoff, M.J.; Bankiewicz, R.; Englund, E.; Ausman, J.; Buerke, A. Long-Term Study of AADC Gene Therapy for Parkinson’s Disease. Hum. Gene Ther., 2012, 23(4), 377-381. http://dx.doi.org/10.1089/hum.2011.220

Marks, W.J.; Bartus, R.T.; Siffert, J.; Davis, C.S.; Lozano, A.; Boullis, N.; Vitek, J.; Stacy, M.; Turner, D.; Veragen, L.; Bakay, R.; Watts, R.; Guthrie, B.; Jankovic, J.; Simpson, R.; Tagliati, M.; Alterman, R.; Stern, M.; Baltuch, G.; Starr, P.A.; Larson, P.S.; Ostrem, J.L.; Nutt; J.; Kieburtz, K.; Kordower, J.H.; Olano, C.W. Gene Delivery of AAV2-Neurintin for Parkinson’s Disease: A Double-Blind, Randomised, Controlled Clinical Trial. Lancet Neurol., 2010, 9(12), 1164-1172. http://dx.doi.org/10.1016/S1474-4422(10)70254-4

Bour, L.J.; Verhagen, R.; Lourens, M.A.J.; de Haan, R.J.; Schuurman, P.R.; de Bie, R.M. Subthalamic Nucleus versus Globus Pallidus Bilateral Deep Brain Stimulation for Parkinson’s Disease (NSTATS Study): A Randomised Controlled Trial. Lancet Neurol., 2013, 12(1), 37-44. http://dx.doi.org/10.1016/S1474-4422(12)70264-8

Khoo, H.M.; Kishima, H.; Horisaki, K.; Maruo, T.; Nani, Oshino, S.; Shimokawa, T.; Yokoe, M.; Mohchuzuki, H.; Saitoh, Y.; Yoshimine, T. Low-Frequency Subthalamic Nucleus Stimulation in Parkinson’s Disease: A Randomized Clinical Trial. Mov. Disord., 2014, 1-5. http://dx.doi.org/10.1002/mds.25810

Contarino, M.F.; Bour, L.J.; Verhagen, R.; Lourens, M.A.J.; de Bie, R.M.A.; van den Munckhof, P.; Schuurman, P.R. Directional Steering: A Novel Approach to Deep Brain Stimulation. Neurology, 2014, 83(13), 1163-1169. http://dx.doi.org/10.1212/WNL.0000000000000823

Merola, A.; Zibetti, M.; Angrisano, S.; Rizzi, L.; Ricchi, V.; Artusi, C.A.; Lanotte, M.; Rizzone, M.G.; Lopiano, L. Parkinson’s Disease Progression at 30 Years: A Study of Subthalamic Deep Brain Stimulation Patients. Brain, 2011, 134(7), 2074-2084. http://dx.doi.org/10.1093/brain/awr121

Albuquerque, L.; Coelho, M.; Martins, M.; Guedes, L.C.; Rosa, M.; Ferreira, J.J.; Cattoni, M.B.; Carvalho, H.; Ferreira, A.G.; Martins, I. F. STN-DBS Does Not Change Emotion Recognition in Advanced Parkinson’s Disease. Parkisonism Relat. Disord., 2014, 20(1), 166-169.

Saez-Zea, C.; Esca Milla-Sevilla, F.; Katati, M.J.; Minguex-Castellanos, A. Cognitive Effects of Subthalamic Nucleus Stimulation in Parkinson Disease: A Controlled Study. Eur. Neurol., 2012, 68(6), 361-366. http://dx.doi.org/10.1159/000341380

Wallace, B.A.; Ashkan, K.; Heise, C.E.; Foste, K.D.; Torres, N.; Mitrofanis, J.; Benabid, A.L. Survival of Midbrain Dopaminergic Cells after Lesion or Deep Brain Stimulation of the Subthalamic Nucleus in MPTP-Treated Monkeys. Brain, 2007, 130(8), 2129-2145. http://dx.doi.org/10.1093/brain/awm137

Spielers-Engemann, A.L.; Steece-Collier, K.; Behbehani, M.M.; Collier, T.J.; Wohlgemut, S.L.; Kemp, C.J.; Cole-Strauss, A.; Levine, N.D.; Gombash, S.; Thompson, V.B.; Lipon, J.W.; Sortwell, C.E. Subthalamic Nucleus Stimulation Increases Brain Derived Neurotrophic Factor in the Nigrostriatal System and Primary Motor Cortex. J. Parkinsons Dis., 2011, 1(1), 123-136.

Palfi, S.; Gururuchag, J. M.; Ralph, G. S.; Lepetit, H.; Lavisse, S.; Buttery, P. C.; Watts, C.; Miskin, J.; Kelleher, M.; Deeley, S.; Iwamuro, H.; Lefaucheux, J. P.; Thiriez, C.; Fenelon, G.; Lucas, C.; Brugières, P.; Gabriel, I.; Abbay, K.; Drouot, X.; Tani, N.; Kas, A.; Gahale, B.; Le Corvoisier, P.; Dolphin, P.; Breen, D. P.; Mason, S.; Guzman, N. V.; Mazarakis, N. D.; Radcliffe, P. A.; Harrop, R.; Kingsman, S. M.; Rascov, O. S.; Naylor, S.; Barker, R. A.; Hantraye, P.; Remy, P.; Cesaro, P.; Mitrophanous, K. A. Long-term safety and long-term vector-based gene therapy for Parkinson’s disease: a dose escalation, open-label, phase 1/2 trial. Lancet, 2014, 383(9923), 1138-1146.
Donoyama, N.; Suoh, S.; Ohkoshi, N. Effectiveness of Anna Massage Therapy in Alleviating Physical Symptoms in Outpatients with Parkinson’s Disease: A before-after Study. *Complement. Ther. Clin. Pract.*, 2014, 20(4), 251-261. http://dx.doi.org/10.1016/j.ctcp.2014.07.010

[206] Cho, S.Y.; Shim, S.R.; Rhee, H.Y.; Park, H.J.; Jung, W.S.; Moon, S.K.; Park, J.M.; Ko, C.N.; Cho, K.H.; Park, S.U. Effectiveness of Acupuncture and Bee Venom Acupuncture in Idiopathic Parkinson's Disease. *Parkinsonism Relat. Disord.*, 2012, 18(8), 948-952. http://dx.doi.org/10.1016/j.parkreldis.2012.04.030

[207] Chae, Y.; Lee, H.; Kim, H.; Kim, C.H.; Chang, D.I.; Kim, K.M.; Park, H.J. Persuading Brain Activity Associated with Acupuncture Treatment in Parkinson's Day Diseasses. *Mov. Res.*, 2009, 24(12), 1794-1802. http://dx.doi.org/10.1016/j.mdr.2009.06.009

[208] Doi, H.; Sakakibara, R.; Sato, M.; Hirai, S.; Masaka, T.; Kishi, M.; Tsuyusaki, Y.; Tateno, A.; Tateno, F.; Takahashi, O.; Ogata, T. Dietary Herb Extract Rikkunshito-Ameliorates Gastroesopahes in Parkinson’s Disease: A Pilot Study. *Eur. Neurol.*, 2014, 71(4-5), 193-195. http://dx.doi.org/10.1159/000355568

[209] Hatano, T.; Hattori, N.; Kawanabe, T.; Terayama, Y.; Suzuki, N.; Iwasaki, Y.; Fujikita, T. An Exploratory Study of the Efficacy and Safety of Yokusankasan for Neuropsychiatric Symptoms in Patients with Parkinson’s Disease. *J. Neural Transm.*, 2014, 121(3), 275-281. http://dx.doi.org/10.1007/s00702-013-1105-y

[210] Li, M.; Liu, Y.; Yang, F.; Ren, F. Effect of Bussen Huoxue Herbs on Depression of Patients with Parkinson’s Disease. *Zhong Yao Cai.*, 2011, 36(8), 1375-1378.

[211] Yang, M.; Li, M.; Dou, Y.; Liu, Y.; Luo, X.; Chen, J.; Shi, H. Effects of Bussen Huoxue Herbal on Motor Function in Patients with Parkinson's Disease: A Multicenter, Randomized, Double-Blind and Placebo-Controlled Trial. *Zhong Yi Xi Jie He Xue Bao.*, 2010, 8(3), 231-237. http://dx.doi.org/10.3736/jcim20100306

[212] Zhang, J.; Ma, Y.; Shen, X. Evaluation on the Efficacy and Safety of Chinese Herbal Medicine Xifeng Dingchan Pill in Treating Parkinson’s Disease: Study Protocol of a Multicenter, Open-Label, Randomized Active-Controlled Trial. *J. Integr. Med.*, 2013, 11(4), 285-290. http://dx.doi.org/10.3736/jijintemed2013036

[213] Jurose, H.L.; LRK2 and Ubiquitin: Implications for Kinase Inhibitor Therapy. *Biochem. J.*, 2015, 470(3), e21-e24. http://dx.doi.org/10.1042/Bj20150785

[214] Golpich, M.; Amini, E.; Hemmati, F.; Ibrahim, A.A.; Dargahi, L.; Ghaseemi, R.; Ahmadiani, A. Glycogen Synthase Kinase 3 Beta (GSK-3β) Signaling: Implications for Parkinson’s Disease. *Pharmacol. Res.*, 2015, 97, 16-26. http://dx.doi.org/10.1016/j.phrs.2015.03.010

[215] Guan, Q.; Liu, X.; He, Y.; Jin, L.; Zhao, L. Effect of Cdk5 Antagonist on L-Dopa-Induced Dyskinesias in a Rat Model of Parkinson’s Disease. *Int. J. Neurosci.*, 2012, 120(6), 421-427. http://dx.doi.org/10.3109/00207484.2012.679769

[216] Cho, S.Y.; Ahmadiani, A.; Dargahi, L.; Ghasemi, D.; Golpich, M.; Amini, E.; Hemmati, F.; Ibrahim, N.M.; Rahmani, B.; Ahmadzadeh, A. Enhancing Dopaminergic Neuron Differentiation of Human Embryonic Stem Cells in a Parkinsonian Rat Model. *PloS One.*, 2011, 6(8), e24027. http://dx.doi.org/10.1371/journal.pone.0024027

[217] Johnson, D.A.; Johnson, J.A. Nrf2—a Therapeutic Target for the Treatment of Neurodegenerative Diseases. *Free Radic. Biol. Med.*, 2015, 89, 253-267. http://dx.doi.org/10.1016/j.freeradbiomed.2015.07.147

[218] Decressac, M.; Volakakis, N.; Björklund, A.; Perlmann, T. NURR1 in Parkinson Disease—from Pathogenesis to Therapeutic Potential. *Nat. Rev. Neurol.*, 2013, 9(11), 629-636. http://dx.doi.org/10.1038/nrneurol.2013.209

[219] Lawand, N.B.; Saadé, N.E.; El-Agnaf, O.M.; Saifiah-Garbedien, B.; Targeting α-synuclein as a therapeutic strategy for Parkinson's disease. *Expert Opin. Ther. Targets.*, 2015, 19(10), 1-10. http://dx.doi.org/10.1517/14728222.2015.1062877

[220] Kethiri, R. R.; Bakhavatchalam, R. Leucine-Rich Repeat Kinase 2 Inhibitors: A Review of Recent Patents (2011 - 2013). *Expert Opin. Ther. Pat.*, 2014, 24(7), 745-757. http://dx.doi.org/10.1517/13543776.2014.907275

[221] LRK2 and Other Novel Exosome Proteins in Parkinson’s Disease. https://www.clinicaltrials.gov/ct2/show/NCT01860118.

[222] Fuji, R.N.; Flagella, M.; Baca, M.; S. Baptista, M.A.; Brodbeck, J.; Chan, B.K.; Fiske, B.K.; Honigberg, L.; Jubb, A.M.; Katavolos, P.; Lee, D.W.; Lewin-Koh, S.C.; Lin, T.; Liu, X.; Liu, S.; Lyssikatos,
J.P.; O’Mahony, J.; Reichelt, M.; Roose-Girma, M.; Sheng, Z.;
Sherer, T.; Smith, A.; Solon, M.; Sweeney, Z.K.; Tarrant, J.;
Urkowitz, A.; Warming, S.; Yaylaoglu, M.; Zhang, S.; Zhu, H.;
Estrada, A.A.; Watts, R.J. Effect of Selective LRRK2 Kinase
Inhibition on Nonhuman Primate Lung. *Sci. Transl. Med.*, 2015,
7 (273), 273ra15-273ra15.

[224] Morales-Garcia, J.A.; Susín, C.; Alonso-Gil, S.; Pérez, D.I.;
Palomo, V.; Pérez, C.; Conde, S.; Santos, A.; Gil, C.; Martínez, A.;
Pérez-Castillo, A. Glycogen Synthase Kinase-3 Inhibitors as Potent
Therapeutic Agents for the Treatment of Parkinson Disease. *ACS
Chem. Neurosci.*, 2013, 4 (2), 350-360. http://dx.doi.org/10.1021/cn300182g

[225] Wang, W.; Yang, Y.; Ying, C.; Li, W.; Ruan, H.; Zhu, X.; You, Y.;
Han, Y.; Chen, R.; Wang, Y.; Li, M. Inhibition of Glycogen
Synthase Kinase-3β Protects Dopaminergic Neurons from MPTP
Toxicity. *Neuropharmacology*, 2007, 52, 1678-1684. http://dx.doi.
org/10.1016/j.neuropharm.2007.03.017

[226] Tolosa, E.; Litvan, I.; Höglinger, G.U.; Burn, D.; Lees, A.; Andrés,
M.V.; Gómez-Carrillo, B.; León, T.; del Ser, T. A Phase 2 Trial of
the GSK-3 Inhibitor Tideglsub in Progressive Supranuclear Palsy.

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