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HIGH IMPACT REVIEW IN NEUROSCIENCE, NEUROLOGY OR PSYCHIATRY - REVIEW ARTICLE

Therapies for Parkinson's diseases: alternatives to current pharmacological interventions

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Abstract Parkinson's disease (PD) is the second most common neurodegenerative disorder caused by the selective and progressive loss of dopaminergic neurons in the substantia nigra pars compacta. Although PD has been heavily researched, the precise etiology and pathogenesis for PD are still inconclusive. Consequently, current pharmacological treatments for PD are largely symptomatic rather than preventive and there is still no cure for this disease nowadays. Moreover, nonmotor symptoms caused by intrinsic PD pathology or side effects induced by currently used pharmacological interventions are gaining increasing attention and urgently need to be treated due to their influence on quality of life. As ancient traditional healing systems, Tai Chi, Yoga, acupuncture and natural products have long been considered as complementary or alternative therapeutic options for PD. Recently, several newly developed non-pharmacological therapeutic strategies, including deep brain stimulation, repetitive transcranial magnetic stimulation, near-infrared light, gene therapy and cell replacement therapy, have also been suggested to give benefits to relieve parkinsonian symptoms. This review will summarize and update the therapeutic potential and the most recent research progresses of these traditional and modern therapeutic options and highlight their clinical meaning for the therapy of not only PD but also other neurodegenerative diseases.

Keywords Cell transplantation · Complementary and alternative therapy · Deep brain stimulation · Gene therapy · Herbal medicine · Parkinson's disease

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide after Alzheimer's disease, affecting 1–2 % of population older than 60 years (Healy et al. 2008; Tarsy 2012). 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 selective and progressive loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (Fahn 2003). PD is believed to be caused by both genetic and environmental risk factors (Warner and Schapira 2003; Verstraeten et al., 2015; Polito et al. 2016). Pathologically, neuroinflammation, mitochondrial dysfunction, protein degradation failure, endoplasmic reticulum stress, and reactive oxygen species overproduction, have been implicated to be involved in PD pathogenesis (Hirsch et al. 2013; Kansara et al. 2013; Shen et al. 2013; Zuo and Motherwell 2013; Tang et al. 2014; Ciechanover and Kwon 2015; Michel et al. 2016). Unfortunately, until now, the precise mechanisms for PD are still largely inconclusive and most PD therapies are symptoms-based rather than preventive or disease-modifying.

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Clinically, motor symptoms are the main features of PD onset and progression, but nonmotor symptoms, including depression, fatigue, hyposmia, sleep disorders, automatic dysfunction, cognitive impairment and dementia, also could be evident in some PD patients. Since 1960s, treatment for PD has been focused on the replacement or supplement of DA. Various DAergic drugs or novel mechanism-based therapeutic candidates have been developed and are subjected into clinical usage or clinical trials for PD treatment (Dong et al. 2016a, b). As the most effective pharmacological medications for PD, levodopa and other DAergic drugs benefit almost all PD patients (Poewe 2009). However, long-term use of levodopa is often accompanied by motor complications, including levodopa-induced dyskinesia (LID) and motor fluctuations, 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, in which the dosage of levodopa should be modified and the formulation of levodopa should be changed to combine with DA agonists or other drugs to control the adverse symptoms. In addition, although some motor dysfunctions of PD, such as tremor and dyskinesia, may be alleviated with drug therapy, characteristics such as postural instability and nonmotor symptoms, especially neuropsychiatric disorders, are less responsive to current medications and require alternative approaches (Nirenberg and Fahn 2005; Schapira and Olanow 2005).

All these above-mentioned limitations of pharmacological treatments generate a notion that non-pharmacological or complementary and alternative management may offer both symptomatic relief and disease-modifications that are beneficial for PD patients. Here, we outline recent studies and summarize evidence on the effectiveness of both traditional and modern therapeutic modalities for PD (Results of clinical trials or meta-analysis of alternative therapies for PD are sumarized in Table1). Moreover, the methodological challenges and possible directions of these therapeutic options for future research are also discussed separately.

Traditional complementary and alternative therapy of PD

Complementary and alternative management of PD is normally defined as a diverse group of therapies, practices or products that share in common their exclusion from conventional and well-accepted medicinal or pharmacological therapies of PD. The variety of traditional complementary and alternative management is increasing yearly, mainly including physio-exercise therapy, Tai chi, Qi gong, relaxation training, acupuncture, traditional herbal medicines, and daily beverage and neutraceuticals.

Physio-exercises therapy

Exercise is an integral part of PD management because physical activity has been shown to retard the deterioration of motor functions, to prolong functional independence and to improve the cognitive disabilities (Lugassy and Gracies 2005; Goodwin et al. 2008; Dibble et al. 2009; Tomlinson et al. 2013, 2014; van der Kolk and King 2013). As for the underlying mechanisms, it has been shown that physio-exercise has a protective effect on the dopaminergic function of PD animals by enhancing neurotrophic factors expression, increasing mitochondrial function and stimulating neuroplasticity (Zigmond and Smeyne 2014; Vivar et al. 2016). More precisely, recent studies further reveal that physio-exercise reduces the alteration of the DAergic neurons in the substantia nigra and contributes toward reconstituting the function of the basal ganglia involved in the motor command through increasing brain-derived neurotrophic factor (BDNF) expression and recovering DA and glutamate neurotransmission (Speelman et al. 2011; Wu et al. 2011), restore mitochondrial function, and attenuate neuroinflammation (Lau et al. 2011), thereafter play neuroprotective roles and restore motor deficits (Frazzitta et al. 2013; Zigmond and Smeyne 2014; Sconce et al. 2015; Svensson et al. 2015; Tuon et al. 2015).

Recent clinical trials have further suggested that aerobic exercise including aerobic walking and stretching could ameliorate motor functions such as gait, balance, physical performance, and nonmotor functions such as fatigue, depression and cognition, but not for fall prevention in PD patients (Uc et al. 2014; Canning et al. 2015). Moreover, it has been reported that intensive training modalities could improve muscle strength and mobility (Cruickshank et al. 2015; Uhrbrand et al. 2015), and low-intensity exercise caused a better performance on gait speed than high-intensity (Shulman et al. 2013). Additionally, resistance-based exercises that address deficits in balance and strength have shown positive effects (Scandalis et al. 2001; Hirsch et al. 2003; Dibble et al. 2006). However, the efficiencies of physio-exercises therapy for PD are not compliant to all clinical symptoms and need more long-term and follow-up studies. In addition, the safety and dose–response relationships (i.e., frequency, intensity, and duration) of physio-exercise therapy for PD are still requires monitoring.

Tai chi and Qi gong

Compared with conventional physio-exercises, Tai chi, an ancient traditional Chinese exercise combining with conscious breath control, relaxation, and slow movements, has been proved effective in reducing balance impairment and falls, with additional functional improvement (Li et al.

2012; Tsang 2013). According to the recent meta-analysis, Tai chi showed positive effects in motor function and balance, but not in gait velocity, step length and gait endurance improvements (Yang et al. 2014). Except for improving motor function, Tai chi could also relieve stress and is beneficial for improving quality of life and mood (Esch et al. 2007; Nocera et al. 2013). It is likely that the benefits of Tai chi are a combination of physical training of strength, balance, stretching, and breathing, and additional improvements in mood and stress. Although the exact mechanisms underlying its therapeutic potential is still barely investigated, Tai chi has been proved to be 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 another traditional Chinese exercise like Tai chi focusing on the movement of internal energy (chi) through the practice of meditation-like practice and focused movements. One randomized controlled trial (RCT) has suggested that Qi gong could improve Unified Parkinson's Disease Rating Scale (UPDRS)-III score, together with several nonmotor symptoms amelioration (Schmitz-Hübsch et al. 2006). In contrast, another small-scale RCT demonstrated that there was no significant motor benefit after Qi gong practice when compared with aerobic training (Burini et al. 2006). Therefore, it still needs more studies to confirm the exact efficacies and explore the best training pattern for anti-Parkinsonism potential of Qi gong.

Mindfulness meditation, Yoga, and other relaxation training

Mindfulness is an ancient spiritual practice as well as a form of stress-reductive meditation training, in which participants are guided towards greater awareness and acceptance of the current moment (Kabat-Zinn 2009). Fitzpatrick et al. (2010) have found that mindfulness has a qualitatively beneficial effect on the PD patients' ability to cope. Subsequently, a quantitative controlled study by Pickut et al. (2015) has suggested an improvement in the observing subscale of the Five Facet Mindfulness Questionnaire (FFMQ) and a reduction in motor disability, but no change in depression measured using the Beck Depression Inventory. In line with previous studies, one recent study found that modified Mindfulness-Based Stress Reduction training improve both motor and nonmotor symptoms of PD, as evidenced by a significant increase in the FFMQ-Observing subscale, a reduction in anxiety and depression scores, an improvement in cognition, a decrease in postural instability and gait difficulty symptomatology, and a reduction in symptom distress observed from the Outcome Questionnaire-45 (Dissanayaka et al. 2016). As for the underlying mechanism for the ameliorating effects of mindfulness against PD, Pickut et al. (2013) have found that, versus non-treated control patients, PD patients subjected to 8 weeks of a mindfulness-based training showed significant increases in gray matter density in the cuneus and lingual gyrus of the left occipital lobe, the left thalamus, the left parahippocampus, and bilaterally in the temporoparietal junction. Most of these brain regions are responsible for emotion, anxiety, and cognitive and motor functioning relevant to PD (Pickut et al. 2013). To date, however, formal evaluations of potential benefits have not been reported. Given the low cost and risk, mindfulness is a reasonable complementary practice to PD patients pending the results of further research testing.

Yoga is a traditional mindfulness-based exercise and is another form of exercise which combines multiple physical elements with relaxation and breathing. It has been shown to significantly improve measures of gait, flexibility, muscle force, fatigue, and quality of life in healthy elderly and people with medical disorders including back pain, arthritis, hypertension, anxiety, and depression. One pilot study has shown that, after 6–12 weeks training, Yoga participants report a significant UPDRS scores improvement and positive trends of ameliorations in tremor, depression scores, body weight and forced expiratory volume (Sharma et al. 2015). Another pilot study has demonstrated that after an 8-week Yoga program, some texts such as sit-and-reach text, single-leg balance text improved significantly, and depression was alleviated to some extent (Boulgarides et al. 2014). Except for these small studies, until now, there is still no big-scale RCT about Yoga in PD treatment. It still requires larger size of individuals and further investigation to ascertain the therapeutic efficiency of Yoga for PD patients.

Besides mindfulness and Yoga, various forms of massage have been indicated to be one of the most common forms of relaxation and alternative therapy for PD (Rajendran et al. 2001). Massage is a broad category that includes different forms of soft tissue manipulation, often incorporated with relaxation. Two months of Japanese massage shows a positive effect in various PD symptoms including shoulder stiffness, muscle pain and fatigue (Donoyama and Ohkoshi 2012). Another before–after study has also suggested that after 40-min Anma massage, the movement difficulties of PD patients were generally improved (Donoyama et al. 2014). A small pilot study of whole body therapeutic massage in PD patients has found an improvement in quality of life and self-reported function (Paterson et al. 2005). Alexander technique uses hand contact to assess and manipulate changes in muscle activity by addressing the relationship between thought and the resultant muscle activity. One RCT of 3-month massage and Alexander technique in 93 PD patients by Stallibrass et al. (2002) has found that, compared with no intervention

control group, the Alexander technique participants show improved on self-assessment disability scores and depression ratings. Reflexology is another form of relax and stress-reductive therapeutic massage and is reported to induce improvements of nonmotor symptoms of PD (Johns et al. 2010). Another study compared massage therapy with simple muscle relaxation techniques and found that massage therapy resulted in significantly lower urinary stress hormone levels, and also self-reported improvements in sleep quality (Hernandez-Reif et al. 2002). In addition, Craig et al. (2006) have demonstrated that neuromuscular therapy, a technique similar to massage but which relies on direct compression of trigger points, was more effective than relaxation at improving motor UPDRS scores in 36 PD patients over a 4-week intervention period. However, these studies did not see a significant increase of urinary DA in PD patients. Moreover, a small RCT recently found that massage significantly reduced salivary cortisol levels in PD patients directly after the treatment, but had no long-lasting effect on diurnal cortisol levels (Törnhage et al. 2013). Although these forms of massage have been shown to be safe and beneficial, larger clinical trials are needed to more fully document their therapeutic efficacy in PD.

Dance and music therapy

Dance is a multi-dimensional activity offering auditory, visual and sensory stimulation, musical experience, social interaction, memory, motor learning and emotional perception, expression and interaction (Kattenstroth et al. 2010). As an intervention for PD patients, dance could improve both motor and nonmotor symptoms. The recent meta-analysis suggests that short-term dance significantly improves UPDRS scores, balance and gait as compared with no intervention controls (Sharp and Hewitt 2014). Dance, especially Tango, has been reported to alleviate motor function and balance, as compared with conventional exercise (Hackney et al. 2007). Additionally, Tango is also thought to offer cognitive benefits such as improving cuing strategies, as it incorporates aerobic activity and movements that challenge gait and balance with progressive motor skill learning in the presence of external cues provided by the partner and the music. Other forms of dance such as waltz/foxtrot, may show similar benefits to Tango in PD (Hackney and Earhart 2009). However, each dance form has different qualities and researchers have hypothesized that certain qualities will target specific PD symptoms. For example, Tango requires frequent movement initiation and cessation, spontaneous directional changes and movement speeds, which may target movement initiation, turning and bradykinesia. In contrast, ballet challenges strength and flexibility to emphasize posture, body alignment, projection of eye focus and limb extension, as well as whole body coordination (Houston and McGill 2013). Although there is sufficient evidence that dance therapy is enjoyable and effective for improving gait and balance in PD patients, long-term outcome data are still lacking. In addition, the safety of dance programs also needs to be adequately reported to ensure the safe and appropriate implementation of dance interventions.

Music therapy uses music or any of its elements (sound, rhythm, melody, or harmony) to facilitate and promote mobilization and expression in order to meet physical, emotional, mental, social, or cognitive requirements. Previous studies have suggested that music may have an ability to impact both motor (including gait and dexterity) and nonmotor (including cognition, anxiety, apathy and depression) functions of PD patients. Pacchetti et al. (2000) have found that the PD patients in the music therapy group show significant improvement in certain motor and quality-of-life measures. de Bruin et al. (2010) also demonstrated improvements in stride length, gait velocity, and cadence among PD patients walking to an individualized playlist compared to controls. Music has been associated with the release of some specific neurochemicals and hormones in both animal and human studies (Möckel et al. 1994; Knight and Rickard 2001; Chanda and Levitin 2013). Additionally, functional magnetic resonance imaging studies have demonstrated an association between music therapy and increased mesolimbic dopamine release (Menon and Levitin 2005).

Acupuncture

Acupuncture, as a vital part of traditional Chinese medicine, has been applies for over 3000 years. In general, acupuncture needle inserted at the specific acupoint stimulates nerve receptors both directly or indirectly, through mechanical coupling via the connective tissues surrounding the needle, then through the local reflex and the central nervous system, induces endocrine, neuroendocrine, autonomic, and systemic behavioral responses. Clinical trials or practices have demonstrated that acupuncture either manual or electro relieves some motor symptoms in PD patients (Yang et al. 2006; Ren 2008; Cho et al. 2012; Toosizadeh et al. 2015) and markedly improves many nonmotor symptoms such as psychiatric disorders, sleep problems, and gastrointestinal symptoms (Cho et al. 2012; Zeng and Zhao 2016). Additionally, previous studies have demonstrated that acupuncture could improved therapeutic efficacy and reduced dosage of levodopa and also ameliorate drugs-induced side effects or complications (Zou 2006; Kim et al. 2014). Acupuncture studies in PD animal models have reported multiple mechanisms for its neuroprotective effects and therapeutic potential. Acupuncture elicited significant recovery and reduced degeneration of substantia

nigra dopaminergic neurons in 6-hydroxydopamine (6-OHDA) lesion rat model (Park et al. 2003). Electroacupuncture may modulate apoptosis and neuroinflammation in the 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) mouse model, suggesting neuroprotective effects (Jeon et al. 2008), possibly via p53-related signaling (Park et al. 2015). Acupuncture or electroacupuncture has also been reported to modulate the expressions of dopamine transporter (DAT) and DA receptors, increase postsynaptic dopamine neurotransmission, and inhibit microglial activation and inflammatory events (Kang et al. 2007; Kim et al. 2011; Rui et al. 2013). Using functional magnetic resonance imaging technique, another randomized trial revealed that acupuncture brought significant improvement of motor function with putamen and primary motor cortex activation, as compared with placebo control groups (Chae et al. 2009). All these findings suggested that acupuncture may serve as a promising complementary and alternative therapy for PD, although more studies, either comparative effectiveness research or high-quality placebo-controlled clinical studies are still warranted.

Traditional herbal medicines

Traditional herbal medicines have been used for centuries. Recent preclinical studies have suggested that some of herbal medicines, either as single agent or in various combinations, may have neuroprotective effects in PD animal models. Ginseng is a plant substance which has been used in Eastern Asian countries for centuries and is proposed to have anti-inflammatory properties, improve fatigue and cognition. Multiple components of Ginseng, such as Rb1, Rg1, Rd, Re, Notoginsenoside R2, and Pseudoginsenoside-F11 have attracted remarkable interest as promising agents due to their beneficial effects in various PD animal models (González-Burgos et al. 2015). These compounds exert their neuroprotective activity through different mechanisms including inhibition of oxidative stress and neuroinflammation, decreases in apoptosis and nigral iron levels, and regulation of *N*-methyl-D-aspartate receptor activity (Wang et al. 2009; González-Burgos et al. 2015; Zhou et al. 2016). *Ginkgo biloba*, as another one widely used herbal medicine with potential antioxidant and neuroprotective properties, has beneficial effects in MPTP animal models (Rojas et al. 2012a, b). The *Ginkgo biloba* extract EGb 761 and its main constituent flavonoids and ginkgolides increase extracellular dopamine levels in the rat prefrontal cortex (Yoshitake et al. 2010). Clinically, a case report has demonstrated that PD patients showed a dramatic improvement after supplementation with ginkgo and a multivitamin–multimineral supplement (Conrad 2014). Interestingly, herbs containing high concentrations of levodopa, such as *Mucuna pruriens* and *Vicia faba*, have been reported to have neuroprotective effects, including recovering endogenous DA production and reducing oxidative stress in the substantia nigra (Manyam et al. 2004; Yadav et al. 2013), and have also been shown to potentially result in less dyskinesia (Rabey et al. 1992; Kasture et al. 2009; Lieu et al. 2010, 2012). Traditional Chinese decoction, San-Huang-Xie-Xin-Tang, composed of *Coptidis rhizoma*, *Scutellariae radix*, and *Rhei rhizoma*, possesses beneficial protection against MPTP model of PD via antioxidative and antiapoptotic effects (Lo et al. 2012). One pilot study reported that dietary extract rikkunshi-to could reduce gastroparesis in terms of shortening gastric emptying time in PD (Doi et al. 2014). Yokukansan is another kind of herbal extract, which is efficient in ameliorating neuropsychiatric symptoms of PD, such as hallucinations, anxiety and apathy, according to a small-scale exploratory trial (Hatano et al. 2014). Through evaluating some neurotransmitters in the brain, Bushen huoxue formulas are considered to enhance the levels of serotonin and norepinephrine, and to improve the depression of PD (Wang et al. 2014). Although previous studies have provided evidence supporting the positive therapeutic potential of herbal medicines for PD, there is still a long way to go for the clinical usage of herbal medicines in PD therapy due to the deficiency of exact bioactive components spectrum data and the lack of sufficient clinical data and safety profile.

Life habits and nutrition supplements

Previous studies have reported an inverse association between cigarette smoking and PD (Morens et al. 1995; Kyrozis et al. 2013). Additionally, numerous case–control studies or cohort studies provide evidence for the protective effect of smoking (Sasco and Paffenbarger 1990; Grandinetti et al. 1994; Gorell et al. 1999; Benedetti et al. 2000; Li et al. 2015). As for the possible mechanisms, previous studies have demonstrated that the anti-PD and neuroprotective effect of cigarette smoking might be due to the reducing enzymatic activity of type B monoamine oxidase (MAO-B) (Fowler et al. 1996), which catabolizes DA and may activate neurotoxicants. Moreover, 2,3,6-trimethyl-1,4-naphthoquinone, one major naphthoquinone component isolated from tobacco, has also been found to exert MAO-B-inhibiting activity and attenuate the DAergic system toxicity in MPTP mouse model (Castagnoli et al. 2001). An animal model further suggests that nicotine, another one major component of cigarette, may act as an antioxidant or prevent excitotoxicity (Halliwell 2006). However, there is no available clinical evidence to indicate that smoking or the use of nicotine and other components of tobacco is beneficial once PD has appeared. Moreover, the healthy concern of tobacco also limits its clinical usage as an alternative therapy for PD.

Similar with smoking, results from epidemiological studies reveal a consistent inverse association between coffee consumption and the risk of PD. A meta-analysis of eight case–control and five cohort studies conducted in four countries between 1968 and 2001 found a 31 % lower risk of PD in coffee drinkers than non-coffee drinkers (Hernán et al. 2002). In addition, this protective potential of coffee against PD shows significant gender preference and hormone sensitivity, as evidenced by the lower PD risk in man and the impacts of postmenopausal hormones on PD risk in women (Ascherio et al. 2003). The protective effect of coffee on PD could be ascribed to caffeine, which is the most important component of coffee and is recently considered as potent Adenosine A2A receptor antagonist. Caffeine and other A2 adenosine receptor antagonists have been shown to stimulate DA release and protect against DAergic neurotoxicity in animal models (Chen et al. 2001; Trevitt et al. 2009; Petzer and Petzer 2015). Although these clinical or preclinical studies have suggested a protective potential of coffee consumption against PD, however, the mechanisms involved are not fully understood and it is premature to recommend increasing coffee consumption to prevent PD, especially in women taking postmenopausal hormones.

In contrast to smoking and coffee, the previously reported relationship between alcohol consumption and PD risk is contradictory. While Palacios et al. (2012) demonstrated that the consumption of beer, wine, or liquor was not associated with PD risk, a more recent meta-analysis of observational studies has revealed an inverse association between alcohol consumption and risk of PD (Zhang et al. 2014). Moreover, multiple lines of evidence have suggested that resveratrol, one natural product present in grape and red wine, could ameliorate neuroinflammation, restor mitochondrial function, reverse oxidative stress over-production, and thereafter provide benefits to various PD animal models (Anandhan et al. 2010; Zhang et al. 2010; Ferretta et al. 2014).

Among the various lifestyle factors, tea consumption has attracted increasing interest, as one of the traditional and most consumed beverages in the world. Previous case–control studies and a cohort study have reported an inverse association between tea drinking and PD risk (Chan et al. 1998; Checkoway et al. 2002; Tan et al. 2003, 2008). Polyphenols components in tea may play important roles in delaying the onset or halting the progression of PD. Green tea and black tea are rich sources of polyphenols, including the most abundant and well-known epigallocatechin-3-gallate (EGCG) and theaflavins. There is now consistent mechanistic data on the neuroprotective and neuroregenerative effects of tea and its major bioactive components (Xu et al. 2006), indicating that they do not just possess anti-oxidant, anti-neuroinflammation or anti-chelating properties (as reviewed by Caruana and Vassallo 2015) but may directly inhibit α-synuclein aggregation and modulate intracellular signaling pathways, both in vitro and in vivo (Bieschke et al. 2010; Camilleri et al. 2013; Chen et al. 2014). However, despite significant data on the potential neuroprotective effects of tea and its bioactive components, clinical studies are still very limited and to date only EGCG has reached phase II trials.

Modern medicine practices that integrate traditional beliefs often focus on nutrition or nutraceuticals, as part of a healthy lifestyle, with the expectation that lowering inflammation and free radical damage may protect against further neuronal death and thus delay or halt disease progression. Evidence from epidemiological studies have been presented that various nutritional supplements, especially vitamins, decrease the risk for PD. For example, vitamin B6 intake has been associated with a significantly decreased risk of PD in smokers (de Lau et al. 2006), vitamin D is also inversely associated with PD (Knekt et al. 2010; Wang et al. 2015). Despite vitamins, other nutraceuticals, such as coenzyme Q10, fish oil and selenium, have shown therapeutic potential for PD. Coenzyme Q10, as the electron acceptor for mitochondrial complexes I and II, can improve complex I activity and reduced levels of coenzyme Q10 have been identified in the mitochondria of PD patients (Shults et al. 1997). However, a phase III trial demonstrates that high-dosage of coenzyme Q10 shows no benefits in early PD (Beal et al. 2014). Similar as coenzyme Q10, although fish oil, glutathione and seletium have been reported to exert antioxidant and anti-neuroinflammation properties, there is still no sufficient evidence to support their clinical usage for PD and the toxicological profiles and side effects of these nutraceuticals should be concerned.

Modern non-pharmacological therapy of PD

Despite those above-mentioned traditional complementary and alternative modalities for PD, recent progress of modern technologies greatly promote the progression of the development of novel strategies for PD therapy. These minimally surgical or non-surgical therapeutic strategies attract attentions and greatly enrich the scope of PD alternative therapy and their clinical benefits for future PD management.

Deep brain stimulation (DBS)

Deep brain stimulation has generally been accepted as an alternative therapy for the amelioration of parkinsonian motor symptoms. Subthalamic nucleus (STN) and globus pallidus internus (GPi), two most hyperactive brain regions

during PD progression, are usually used as targets for DBS. In addition, STN-DBS could be preferred to manage patients with advanced PD who have predominantly posture and gait disorders due to its larger improvements in off time (Odekerken et al. 2013). The beneficial effects of DBS on appendicular symptoms such as tremor, rigidity, limb bradykinesia and dyskinesia are well established (Roper et al. 2016), although the exact underlying mechanisms for DBS still remain poorly understood. After long-term observation, both STN- and GPi-targeted DBS therapy showed significant improvement in "on–off" conditions, dyskinesias and motor fluctuations (Weaver et al. 2012; Rizzone et al. 2014). Recently, DBS treatment at 60 Hz frequency shows a promising application potential to improve swallowing, gait freezing, and axial motor signs, almost overall motor signs of PD (Khoo et al. 2014; Xie et al. 2015). Despite the STN and Gpis, DBS therapy with pedunculopontine tegmental nucleus (PPNs) as stimulation targets has recently been found to be an alternative to STN-DBS (Follett et al. 2012; Katz et al. 2015). Moreover, a novel 32-contact electrode of DBS, brings more potential benefits via widened therapeutic window and increased effectiveness (Contarino et al. 2014). As for the mechanisms for therapeutic potential of DBS against PD, preclinical trials, by using either non-human primates or other mammalian species, have shown that there is an improvement of DAergic neurons survival and an increase of BDNF level in the substantia nigra and primary motor cortex after STN-DBS exposure, suggesting the neuroprotective effect of DBS (Wallace et al. 2007; Spieles-Engemann et al. 2011). The local effects of DBS tend to result in the inhibition of neuronal-cell bodies and the excitation of neighboring axons. In addition, astrocytes are stimulated to release calcium, which may lead to a release of glutamate and adenosine, improved microvascular integrity, as well as local increases in cerebral blood flow. Finally, there is evidence that deep brain stimulation can induce local and possibly distal proliferation of neural precursor cells (Okun 2012; Pienaar et al. 2015). From a neurophysiological view, the "disruption hypothesis" seems to be more and more accepted, in which DBS dissociates input and output signals, resulting in the disruption of abnormal information flow through the stimulation site (Chiken and Nambu 2016). Although gross motor improvement is frequently observed following DBS therapy in PD, lack of uniformity in methodology and measured outcomes has clouded the interpretation of DBS benefits across the motor domain. In addition, despite these therapeutic benefits to motor performance of PD, the effects of DBS on nonmotor cognitive and psychiatric symptoms of PD have been controversial. A progressive worsening of neuropsychological performance and movement disorder are even observed (Merola et al. 2011; Baizabal-Carvallo and Jankovic J 2016), although some scholars consider the impairment of neurocognition might be due to the disease progress and medication reduction, not the DBS itself (Sáez-Zea et al. 2012; Weaver et al. 2012; Albuquerque et al. 2014). Finally, further large sample size trials for brain target site analyses should be performed for clarify the different therapeutic outcomes of various DBS stimulation targets, including STN, GPi and PPNs (Diamond and Jankovic 2005; Baizabal-Carvallo and Jankovic 2014).

Repetitive transcranial magnetic stimulation (rTMS)

Surgical therapies, including DBS, improve advanced symptoms above the best medical therapy, however, only limited (less than 5 %) PD population is suitable candidates for this surgical procedure (Morgante et al. 2007). During the past two decades, rTMS has been closely examined as a possible therapeutic option for PD (Pascual-Leone et al. 1994a, b; Fregni et al. 2005; Elahi et al. 2009). As a noninvasive therapeutic procedure, rTMS delivers repeated magnetic pulses to a specific brain area within a short time through a stimulation coil placed over the scalp without surgery or anesthesia. The repeated magnetic pulses not only alter excitability at local site of stimulation but also influence distant brain regions via the cortico-basal ganglia-thalamo-cortical motor circuit (Strafella et al. 2001; Kim et al. 2008; González-García et al. 2011). Additionally, different types of rTMS may cause different response of cortical excitability. For examples, while high-frequency rTMS induces cortical excitability (Pascual-Leone et al. 1994a, b), low-frequency rTMS causes a depressed cortical activity (Chen et al. 1997). Continuous high-frequency rTMS decreases cortical excitability, whereas intermittent high-frequency rTMS increases cortical excitability (Huang et al. 2005). Because rTMS can produce changes in neural activity and motor signs last well after stimulation, this technique has generated much interest as a potential therapeutic intervention for patients with PD and many rTMS trials have been uptaken to investigate its clinical benefits (Chou et al. 2015; Zanjani et al. 2015). Moreover, several types of rTMS were reported to be effective for drugs-induced dyskinesia and also been tried for non-pharmacological treatment of non-motor symptoms of PD including depression (Shirota et al. 2016). One most recent meta-analysis further advocates the beneficial effect of rTMS on upper limb function in the short term and on walking performance and motor signs measured by UPDRS III in both the short- and long terms (Chung and Mak 2016). The use of rTMS has a minimal risk of adverse events in the PD patient population and should be encouraged as an alternative treatment for PD so long as it is thought to produce clinically relevant

improvements in motor functions. However, the potential risk for seizure as well as a small risk of transient headache and scalp pain should be concerned (Vonloh et al. 2013).

Near-infrared light (NIr) therapy

NIr has been applied in clinical practice mainly for treating tissue contusion for many years. There have also been many in vivo studies of NIr-induced neuroprotection in various PD animal models. Previous preclinical studies have demonstrated that NIr could improve behavior deficits and DAergic neurons survival in parkinsonian mice (Shaw et al. 2010; Johnstone et al. 2014; Moro et al. 2014; Reinhart et al. 2015a, b; El Massri et al. 2016). Remarkably, a recent primate trial has further supported the notion that NIr was neuroprotective but not toxic to brain, which brought a step closer to clinical translation (Darlot et al. 2016). Although substantial evidence supports the therapeutic efficacy of NIr in PD animal models, there have been only limited research reports to date on the efficacy of NIr treatment in PD patients. There is a recent non-controlled and non-randomized clinical report indicating improved speech, cognition, freezing episodes and gait after extracranial NIr therapy in PD patients (Maloney et al. 2010); there are also some clinical reports suggesting improvements in parkinsonian signs in PD patients after intranasal NIr therapy (Zhao et al. 2003). We should note that extracranially delivered NIr may not reach the zones of pathology in the brainstem of PD patients and would only provide symptomatic effects. Hence, an intracranial system might be developed and suggested for PD patients to play neuroprotective and disease-modifying roles to maximize its therapeutic effects.

Neurotrophic factors (NTFs) therapy

Most of the current pharmacological therapies for PD focus on managing symptoms, rather than the molecular pathogenic causes. Therefore, the greatest unmet demand in PD therapy is to discover and develop disease-modifying strategies, which can halt or reverse the ongoing progression of dopaminergic neurons degeneration. One of the promising candidates for disease-modifying therapies is NTFs. NTFs are secreted growth factors that regulate survival, growth, differentiation and maintenance of neurons in both the central nervous system and the peripheral nervous system. Although many animal research suggesting the therapeutic potential of neurotrophic factors for treating neurodegenerative diseases, the clinical trials have not produced conclusive evidence to supporting their utilities as therapies (for reviews see Sullivan and Toulouse 2011; Hegarty et al. 2014; Bartus and Johnson 2016a, b). Following the series of disappointing outcomes from systemic administration of NTFs, including GDNF, CNTF, BDNF and IGF-1, to improve their therapeutic efficiency, NTFs was later tested using intrathecal, Intraventricular or intraparenchymal delivery. However, these types of delivery are associated with several practical problems, such as the poor targeting and rapid biometabolism of NTFs by endogenous enzymes in vivo. Gene therapy can overcome these limitations by incorporating the gene for the therapeutic protein into brain cells, achieving long-term and targeted delivery. Recombinant adeno-associated viral (AAV) or lentiviral vectors (LV) have been used to induce over-expression of NTFs in animal models of PD (for recent review see Kelly et al. 2015) and led to considerable advancements in the ongoing development of clinical neuroprotective therapies for PD. However, in contrast to the successful studies which used GDNF in the 6-OHDA lesion rat models, GDNF delivery by either AAV or LV vectors was not effective in preventing neurodegeneration in the AAV-α-synuclein model (Decressac et al. 2011). Further investigation demonstrated that α-synuclein overexpression downregulates the expression of Nurr1 and its downstream target, the GDNF receptor Ret, in DA neurons of the SN (Decressac et al. 2012). These findings suggest that the development of DAergic NTFs might be Ret-dependent and Ret/NTFs combined gene delivery approach or other Ret-independent NTFs should be explored (Sullivan and O'Keeffe 2016).

Gene therapy

In general, gene therapy methodology is achieved by counteracting or replacing a malfunctioning gene within the cells adversely affected by the condition. For the most part, viruses-based vectors are used to deliver therapeutic molecules including glutamic acid decarboxylase (GAD), aromatic L-amino acid decarboxylase (AADC), neurturin, and neurotrophic factors by now. A phase 1/2 trial with one-year follow-up has shown that ProSavin, a LV vector-based gene therapy to deliver tyrosine hydroxylase, GAD and AADC, significantly improves UPDES-III scores of PD patients without serious side effects (Palfi et al. 2014). Transfer of GAD with AAV2 can modulate γ-aminobutyric acid production with a great improvement of UPDRS scores over 6 months as well (LeWitt et al. 2011). Others like AAV2-hAADC and AAV2-neurturin (CERE-120) have also shown the similar therapeutic benefits and safety profiles (Marks et al. 2010; Mittermeyer et al. 2012; Bartus et al. 2013). Moreover, modified virus-based vectors and non-virus vectors are developed constantly. For examples, tropism-modified Ad5 vectors exert neuron-selective targeting property to enhance gene delivery efficiency (Lewis et al. 2014). Angiopep-conjugated nanoparticles for cellular uptake and gene expression can carry specific genes (Huang et al. 2013). A recently developed non-viral vector

Table 1 Results of clinical trials or meta-analysis of alternative therapies for PD

	Treatment	Sample size	Reported results	Ref.
Physio-exercise	Mixed exercise (4–12 weeks)	14 RCTs	Exercise is effective in improving physical functioning, QoL, leg strength, balance, and gait. Insufficient evidence that exercise improves falls and depression	Goodwin et al. 2008
	Mixed exercise (3–12 weeks)	16 studies (13 RCTs)	Improvement in postural instability and balance task performance. Limited evidence to support improvement in QoL and insufficient evidence that it can affect near-falls and falls	Dibble et al. 2009
	Aerobic walking (6 months)	60 patients	Improvements in maximum oxygen consumption, gait speed, UPDRS I and III scores, fatigue, depression, quality of life, and flanker task scores	Uc et al. 2014
	Balance and lower limb strengthening (6 months)	231 patients	Improvements in physical and psychological health. Falls were reduced in people with milder disease but not in those with more severe PD	Canning et al. 2015
	Treadmill, stretching and resistance training (3 months)	67 patients	The lower-intensity treadmill exercise resulted in the greatest improvement in gait speed. Both the higher- and lower-intensity treadmill exercises improved cardiovascular fitness. Only the stretching and resistance exercises improved muscle strength	Shulman et al. 2013
	Resistance training (8 weeks)	14 patients	Produce functional improvements in gait	Scandalis et al. 2001
	Balance and resistance training (10 weeks)	15 patients	Muscle strength and balance can be improved by high-intensity resistance training and balance training	Hirsch et al. 2003
Tai chi & Qi gong	Tai chi (24 weeks)	195 patients	Reduced balance impairments in patients with mild-to-moderate PD, with additional benefits of improved functional capacity and reduced falls	Li et al. 2012
	Tai chi (24 weeks)	195 patients	Tai chi is effective in reducing balance impairments in patients with mild to moderate PD	Tsang 2013
	Tai chi (4–24 weeks)	8 studies (7 RCTs)	Improved motor function, balance and functional mobility in patients with PD, but not gait velocity, step length, or gait endurance	Yang et al. 2014
	Tai chi (18 weeks)	21 patients	Subjective health increased, stress decreased (objectively and subjectively) during Tai Chi practice	Esch et al. 2007
	Tai chi (16 weeks)	15 patients	Significantly better scores on the PDQ-39 total score as well as the emotional well-being sub score. Trends for improvement on Digits Backwards, Tinetti's Falls Efficacy Scale, and the activities of daily living and communication sub scores of the PDQ-39	Nocera et al. 2013
	Qi gong (4 months)	56 patients	Ameliorated progression of motor symptoms as assessed by UPDRS-III. Decreased incidence of several nonmotor symptoms.	Schmitz-Hübsch et al. 2006
Mindfulness, Yoga & massage	Mindfulness-based cognitive therapy (8 weeks)	12 patients	Help people in coping with stress, confidence, negative thinking, social relationships, and reinforce practical coping with PD	Fitzpatrick et al. 2010
	Mindfulness based intervention (8 weeks)	27 patients	Decreased UPDRS motor score, increased PDQ-39 pain item, and increased FFMQ observe facet	Pickut et al. 2015
	Mindfulness intervention (8 weeks)	14 patients	A significant increase in FFMQ-Observe subscale, a reduction in anxiety, depression, and OQ-45 symptom distress, an increase in PDCRS-Subcortical scores, and an improvement in postural instability, gait, and rigidity motor symptoms	Dissanayaka et al. 2016
	Yoga (12 weeks)	15 patients	Significant improvement in UPDRS scores, diastolic blood pressure and average forced vital capacity. Positive trends of improvement were noted in depression scores, body weight and forced expiratory volume. Yoga participants reported more positive symptom changes including immediate tremor reduction	Sharma et al. 2015
	Yoga (8 weeks)	10 patients	The depression subscale of the HADS, the TSCS, the SLB, and the right and left SRT were changed following the yoga intervention	Boulgarides et al. 2014
	Traditional Japanese massage (8 weeks)	10 patients	Improved gait speed, improved range of motion of the shoulder joint, and improved VAS scores	Donoyama and Ohkoshi 2012

Table 1 continued

	Treatment	Sample size	Reported results	Ref.
	Anma massage (single session or 7 weeks session)	21 patients	Visual analogue scale scores were significantly lower for muscle stiffness, movement difficulties, pain, and fatigue; gait speed and pegboard test time were significantly shortened; stride length was significantly lengthened; and shoulder flexion and abduction were significantly improved	Donoyama et al. 2014
	Deep whole body massage (8 weeks)	10 patients	Improvement in self-confidence, well-being, walking and activities of daily living	Paterson et al. 2005
	Alexander Technique (12 weeks)	93 patients	Improved SPDDS. Less depressed post-intervention on the Beck Depression Inventory	Stallibrass et al. 2002
	reflexology treatments (8 sessions over 20 weeks)	16 patients	Improvement in wellbeing over the active therapy phase	Johns et al. 2010
	Massage (10 sessions over 5 weeks)	16 patients	Improvment in daily living activities, daily functioning, and having more effective and less disturbed sleep. Lower urine norepinephrine and epinephrine levels	Hernandez-Reif et al. 2002
	neuromuscular therapy (4 weeks)	36 patients	Significant and sustained improvement in the Motor subscale of the UPDRS, most notable in the tremor scores. Improved CGI scores and the finger-tapping speed. No effect on mood. No group difference in PDQ-39 scores or in nonmotor measures	Craig et al. 2006
Dance & music	Dance (Tango or Irish, 13, 26 or 52 weeks)	5 studies	Improved UPDRS motor scores, berg balance and gait speed. Improvements in berg balance and quality of life (PDQ-39)	Sharp and Hewitt 2014
	Tango (20 lessons in 13 weeks)	19 patients	Significant improvment on motor subscale 3 of the UPDRS. Improvement on the Berg Balance Scale. There was no significant change in perception of freezing; slight, non-significant changes in gait velocity and also showed virtually no change in dual-task walking velocity	Hackney et al. 2007
	Tango, waltz/foxtrot (20 lessons in 13 weeks)	58 patients	The tango and waltz/foxtrot groups improved significantly on the Berg Balance Scale, 6-minute walk distance, and backward stride length. The tango group improved as much or more than those in the waltz/foxtrot group on several measures	Hackney and Earhart 2009
	Music therapy (13 weeks)	32 patients	Music therapy had a significant overall effect on bradykinesia as measured by the UPDRS. Improvements in emotional functions, activities of daily living and in quality of life	Pacchetti et al. 2000
	Walking with music (13 weeks)	22 patients	Improved gait velocity, stride time, cadence, and motor symptom severity following the intervention	de Bruin et al. 2010
Accupuncture	Accupuncture (4 courses × 10 times)	38 patients	Significantly decreased UPDRS score after 4 courses accupuncture plus drugs therapy compared with drugs therapy.	Yang et al. 2006
	Accupuncture (2 courses × 10 times)	50 patients	Obvious alleviation of motor disorder in the accupuncture plus Medopar treatment group, which was significantly higher than Medopar group	Ren 2008
	Acupuncture and bee venom acupuncture (8 weeks)	43 patients	Bee venom acupuncture showed significant improvement on the UPDRS (total score, parts II and III), the Berg Balance Scale, and the 30 m walking time. Acupuncture showed significant improvement on UPRDS (part III and total scores) and the Beck Depression Inventory	Cho et al. 2012
	Electroaccupuncture (3 weeks)	15 patients	Improved balance performance, reduced COGML/AP sway, increased ankle/hip sway. Overall improvement in mentation, behavior, and mood (UPDRS I), activities of daily living (UPDRS II), and motor examination (UPDRS III). Significant reduction in the specific items regarding UPDRS fall status and rigidity	Toosizadeh et al. 2015
Herbal medicine	Herb extract rikkunshi-to (15.0 g/day, 12 weeks)	20 patients	Significant shortening of the gastric emptying time	Doi et al. 2014
	Yokukansan (7.5 g/day, 12 weeks)	25 patients	Significantly decreased median neuropsychiatric inventory (NPI) total score; significant improvements in hallucinations, anxiety and apathy; The positive symptoms (delusions-hallucinations-irritability) significantly decreased; negative symptoms (anxiety-apathy) significantly decreased. Both UPDRS-III and the Hoehn and Yahr scale showed no significant change	Hatano et al. 2014
	Bushen Huoxue Granule (40 g/day, 12 weeks)	62 patients	The scores of Hamilton depression rating scale were decreased markedly. Reversed the declined norepinephrine and 5-serotonin levels in brain of PD patients	Wang et al. 2014

Table 1 continued

	Treatment	Sample size	Reported results	Ref.
Life habits	Smoking	69 studies	The pooled relative risk of PD was 0.59 for ever smokers compared with never smokers. The summary relative risk for those smoking more than 30 pack-years was 0.66, and 0.39 for those smoking less than 30 pack-years	Li et al. 2015
	Smoking	196 patients	The relative risk for cigarette smoking was 0.69	Benedetti et al. 2000
	Smoking	144 patients	Inverse association between current light smokers (>0 to 30 pack-years) and PD patients (odds ratio 0.59), and a stronger inverse association of PD with current heavy smokers (>30 pack-years; odds ratio 0.08)	Gorell et al. 1999
	Smoking	8006 patients	A reduced risk of developing idiopathic PD (relative risk = 0.39)	Grandinetti et al. 1994
	Coffee	13 studies	Compared with non–coffee drinkers, relative risk of PD was 0.69 for coffee drinkers. The relative risk per three additional cups of coffee per day was 0.75 in case–control studies and 0.68 in cohort studies	Hernán et al. 2002
	Coffee	154 patients	Use of hormones was associated with a reduced risk of PD among women with low caffeine consumption (RR 0.39), and with increased risk among women with high caffeine consumption (RR 2.44). Among hormone users, women consuming six or more cups of coffee per day had a four fold higher risk of PD (RR 3.92) than did women who never drink coffee	Ascherio et al. 2003
	Alcohol	605 patients	Alcohol consumption was not significantly associated with PD risk	Palacios et al. 2012
	Alcohol	32 studies	A significant association was found with beer (0.59) but not with wine and liquor, and for males (0.65) after a sensitivity analysis but not for females. The risk of PD decreased by 5% for every 1 drink/day increment in alcohol intake in a linear dose-response manner	Zhang et al. 2014
	Tea	300 patients	Amount of tea drunk (OR 0.724) to be significant factors associated with PD. One unit of tea (3 cups/day for 10 years) would lead to 28% risk reduction of PD	Tan et al. 2003
	Tea	157 patients	Black tea showed an inverse association with PD risk. Green tea drinking was unrelated to PD risk	Tan et al. 2008
	Tea	210 patients	Reduced risks were observed for consumption of 2 cups/day or more of tea (OR 0.4)	Checkoway et al. 2002
Nutritions	Vitamine B6	6969 participants	Higher dietary intake of vitamin B6 was associated with a significantly decreased risk of PD	de Lau et al. 2006
	Vitamine D	8000 participants	Individuals with higher serum vitamin D concentrations showed a reduced risk of PD	Knekt et al. 2010
	Vitamine D	478 patients	Inverse association between vitamin D levels and PD	Wang et al. 2015
	CoQ10	17 patients	Level of coenzyme Q10 was significantly lower in mitochondria from PD patients; levels of coenzyme Q10 and the activities of complex I and complex II/III were significantly correlated	Shults et al. 1997
	CoQ10 (1200– 2400 mg/d)	267 patients	Coenzyme Q10 was safe and well tolerated in this population, but showed no evidence of clinical benefit	Beal et al. 2014
DBS	GPi DBS and STN DBS	128 patients	STN could be the preferred target for DBS in patients with advanced PD	Odekerken et al. 2013
	STN DBS	27 studies	Both unilateral and bilateral DBS provide a therapeutic benefit on gait speed in persons with PD	Roper et al. 2016
	STN DBS (10–13 years)	26 patients	Significantly improved motor symptoms; Motor complications were well controlled, with improvements of dyskinesias and motor fluctuations. The UPDRS-II-on score worsened	Rizzone et al. 2014
	GPi DBS and STN DBS (36 months)	159 patients	The beneficial effect of DBS on motor function was stable and comparable	Weaver et al. 2012
	STN DBS (6 weeks)	7 patients	Compared with the routine 130 Hz, the 60-Hz stimulation significantly improved swallowing function, FOG, and axial and parkinsonian symptoms in patients with PD	Xie et al. 2015
	STN DBS	14 patients	Low-frequency stimulation via the optimal contacts is effective in improving overall motor function of patients with PD	Khoo et al. 2014
	Steering DBS	8 patients	Steering DBS current is well tolerated, increases the threshold for side effects, and may improve the therapeutic window of STN DBS	Contarino et al. 2014

Table 1 continued

	Treatment	Sample size	Reported results	Ref.
TMS	TMS	12 studies (224 patients)	TMS, across applied stimulation sites and parameters, can exert a significant, albeit modest, positive effect on the motor function of patients with PD	Fregni et al. 2005
	rTMS	20 studies (470 patients)	rTMS improves motor symptoms for patients with PD. Combinations of rTMS site and frequency as well as the number of rTMS pulses are key modulators of rTMS effects	Chou et al. 2015
	rTMS (single or multiple sessions)	11 studies (246 patients)	Compared with sham rTMS, active rTMS targeting primary motor cortex significantly improved UPDRS III scores at the short-term follow-up	Zanjani et al. 2015
	rTMS	22 trials (555 patients)	rTMS improves upper limb function in the short-term, walking performance and UPDRS III in the short- and long-terms in PD sufferers	Chung and Mak 2016
Gene and cell replacement therapy	ProSavin	15 patients	ProSavin was safe and well tolerated in patients with advanced PD. Improvement in motor behaviour was observed in all patients	Palfi et al. 2014
	AAV2-GAD	22 patients	Decreased UPDRS score for the AAV2-GAD therapy	LeWitt et al. 2011
	AAV2-neurturin	58 patients	There was no significant difference in the primary endpoint in patients treated with AAV2-neurturin compared with control individuals	Marks et al. 2010
	AAV2-neurturin	6 patients	Bilateral neurturin gene delivery (CERE-120) to the SN plus putamen in patients with moderately advanced PD is feasible and safe	Bartus et al. 2013
	AAV2-hAADC	10 patients	The UPDRS in all patients off medication for 12 hr improved in the first 12 months, but displayed a slow deterioration in subsequent years	Mittermeyer et al. 2012
	Bone-marrow-derived mesenchymal stem cells transplantation	7 patients	Steady improvement in their "off"/"on" UPDRS; Hoehn and Yahr and Schwab and England scores showed similar improvements; A subjective improvement was found in symptoms like facial expression, gait, and freezing episodes	Venkataramana et al. 2010

has been found to deliver short interfering RNA (siRNA) against the α-synuclein gene specific for neuronal cells, and prevent PD-like symptoms both in vitro and in vivo. Interestingly, this non-viral vector not only helps siRNA duplexes cross the blood–brain barrier in mice, but also stabilize these siRNAs leading to a sustainable knockdown of α-synuclein protein (Javed et al. 2016). Although recent clinical trials of gene therapy have shown remarkable therapeutic benefits and an excellent safety record, however, at this time, no study has demonstrated robust clinical benefits using rigorous double-blind assessments. In addition, as currently practiced, gene therapy for PD only addressed the cardinal motor symptoms, and the possible impacts of gene therapy on other clinical signs of PD should be further investigated.

Cell replacement therapy

Cell transplantation is available nowadays and numerous preclinical studies and several clinical trials have shown therapeutic effects of various types of stem cell transplantation, such as motor signs improvement or medication dosage reduction (O'Keeffe et al. 2008; Venkataramana et al. 2010; Gonzalez et al. 2015a, b; Han et al. 2015). Although transplantation of stem cells-derived DAergic neuron can alleviate motor deficiencies of PD, previous studies also found that tumor formation was an unacceptable complication associated with stem cells, especially embryonic stem cells (ESCs) transplantation (Bjorklund et al. 2002; Kim et al. 2002). To minimize the risk of tumor formation, a number of techniques have been developed, including prolonged pre-differentiation of ESCs, selection of differentiated cells for transplantation and genetic engineering to block tumourigenic pathways (Ambasudhan et al. 2014). In addition, Acquarone et al. (2015) pretreated undifferentiated mouse ESCs with mitomycin, then injected into striatum in nude mice. After 15-month follow-up, mitomycin-treated ESCs alleviated motor functions dramatically without unlimited cell proliferation that would be a novel replacement therapy for PD. Besides, reprogrammed neurons, such as combination of new transcriptional therapy may decrease the tumorigenic potential (Yamashita and Abe 2014). Using human unfertilized cell or induced pluripotent stem cells (iPSCs) also offers an unlimited supply for transplantation. The animal experiments confirm its safety and efficiency on motor symptoms (Gonzalez et al.

2015a, b; Han et al. 2015). In a long-term 14-year observation after DAergic neuron transplantation, the majority of transplanted neurons maintain healthy and functional, as shown by the persistent expression of DA transporters and normal mitochondrial morphologies, which proves the rationality and feasibility of cell transplantation as alternative therapy in PD (Hallett et al. 2014). Although many types of stem cells, such as ESCs, iPSCs and NSCs, have been induced into DAergic neurons for PD treatment in various animal models, so far few has been clinically proved functional for patients with PD. Besides the tumorigenic potential, the cell sources, optimal transplantation protocols, including reliable delivery system, transplantation locations and timing, also need to be further explored before clinical use of stem cells-derived DAergic neurons for the transplantation into PD patients.

Environmental enrichment (EE)

Enriched environments are normally defined as a combination of complex inanimate and social stimulation. For rodent studies, EE is generally constituted by bigger cages, with a running wheel and a few toys that are periodically changed to stimulate animal curiosity and exploration. Previous studies have suggested that EE could protect brain damage and promote neuroplasticity in various neurodegenerative animal models including PD. Faherty et al. (2005) have demonstrated that exposure to an EE procedure (a combination of exercise, social interactions and learning) during adulthood totally protects against MPTP-induced Parkinsonism. Furthermore, this neuroprotection of dopamine neurons in the nigrostriatal system might be due to the increased GDNF and decreased DAT and vesicular monoamine transporter (VMAT2) levels (Faherty et al. 2005; Zhu et al. 2005). Similar neuroprotective effects of enriched environment in PD have also been confirmed in 6-OHDA animal model (Steiner et al. 2006; Anastasía et al. 2009). Although all these preclinical findings predict significant implications of this non-pharmacological approach for the prevention and/or treatment of PD, the exact molecular mechanisms are far from being clearly understood. Much more importantly, till now the clinical efficacy of EE therapy in PD patients is rarely reported. Moreover, the containing elements and the training procedure in EE therapy for PD should be further explored before the translation of this non-pharmacological modality from benchside to bedside.

Conclusion

PD patients exhibit various degrees of motor impairment as well as nonmotor symptoms which include depression, apathy, cognitive impairment, sleep disturbances, and autonomic dysfunctions. In the absence of any disease-modifying therapy, the mainstay of PD treatment is pharmacologic therapy aimed at replacement of DAergic function. While this is generally effective for motor symptoms, long-term medication may fail to treat, or even worsen, troublesome nonmotor symptoms and may lead to motor complications. It is not surprising then that nearly 40 % of PD patients in US were using complementary and alternative practices in addition to or instead of conventional treatment options (Rajendran et al. 2001). Centuries of experience using conventional medical modalities (such as herbal medicines and acupuncture) and traditional physical training (includes Tai chi, Qi gong and Yoga) in Eastern countries have been proved to be effective to relieve some of PD symptoms via various mechanisms. In addition, the rapid development of modern science and technology has add new meaning into this traditional remedies and greatly promote the discovery of novel non-pharmacological therapies of PD, including DBS, NIr, gene therapy and cell replacement therapies, as well as some other complementary management (Fig. 1). All these newly developed therapeutic options have been demonstrated to be able to provide potential clinical benefits to patients with PD to relieve either motor or nonmotor deficiencies or drugs-induced side effects. Much more importantly, following the clinical usage of these alternative therapeutic options, we could learn more about the precise pathogenic mechanisms of PD and found more therapeutic targets by which to discover more disease-modifying drugs. In addition, it is proposed that these new therapies may bring promise to give new cures to not only PD, but also other neurodegenerative diseases

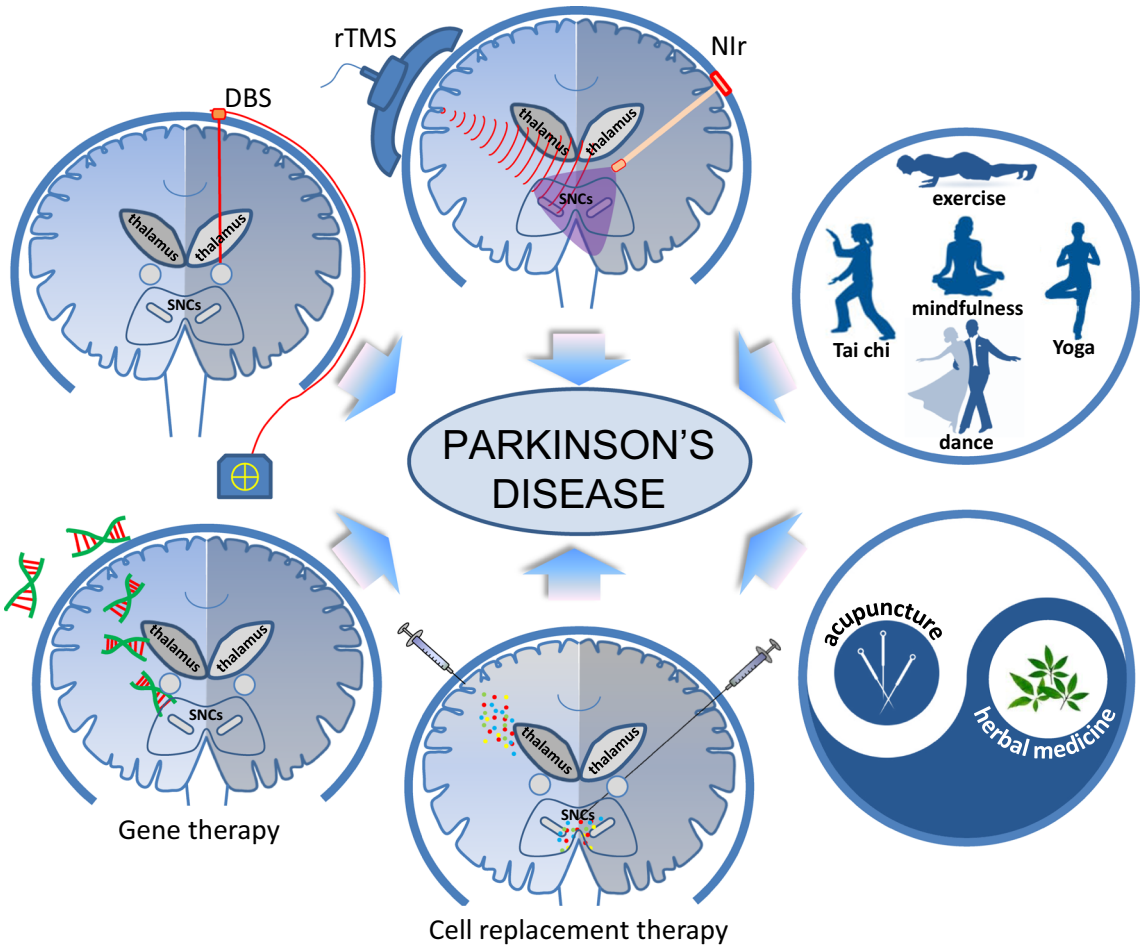

Fig. 1 Complementary and alternative therapies of Parkinson 's disease

(Nithianantharajah and Hannan 2006; Perlmutter and Mink 2006; Ljubisavljevic et al. 2013; Soligo et al. 2013).

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Compliance with ethical standards

Conflict of interest The author(s) confirm that this article content has no conflict of interest.

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