Movement Disorders
CLINICAL PRACTICE
REVIEW

Complementary Therapies for Parkinson's Disease: What's Promoted, Rationale, Potential Risks and Benefits

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Abstract: **Background:** Nearly half of all patients with Parkinson's disease (PD) utilize some form of complementary therapy often identified on the Internet and frequently not reported to their physicians. Treating physicians are sometimes unaware of such treatments, including their rationale, mechanisms, potential efficacy, and potential adverse effects.
Methods: Methods for this study included systematic Internet search of products recommended for PD, medical literature review to determine scientific rationale, any evidence of efficacy, and potential risks.
Results: A large number of complementary therapies are recommended for patients with PD, generally falling into the following categories: dietary and nutritional; chelation; and physical. Most have reasonable justifications based on mechanism of action and current theories on causes of neurodegeneration in PD, but few have documented evidence of benefit. Fortunately, most have few risks and side effects, although some are very expensive. The protein redistribution diet has substantial evidence of symptomatic benefit. Some antioxidative or -inflammatory supplements, aerobic exercise, Tai chi, and dance and music therapy have preliminary evidence of symptomatic benefit or potential neuroprotective effects, but more research is needed to establish efficacy.
Conclusions: Patients with PD are faced with many recommendations for complementary therapies. Physicians should know about these in order to have informed discussions with their patients. Some deserve further study.

Although current treatments for Parkinson's disease (PD) are often very effective, they do not influence the underlying neurodegenerative process, are frequently less effective over time, may lead to unwanted side effects, and can be costly or invasive. For these reasons, patients with PD often seek so-called complementary therapies for their disease.

According to the National Institute of Health (NIH), the term "complementary" generally refers to a nonmainstream approach used in conjunction with conventional medicine. "Alternative" and "integrative" are sometimes used interchangeably with complementary, but the NIH defines alternative therapy as a treatment used in place of mainstream medicine, and integrative medicine as when both mainstream and nonmainstream treatments are prescribed by a provider to be used together. Most of the nontraditional therapies are used by PD patients in conjunction with traditional treatments, and thus we use complementary to describe these treatments here.

It has been estimated that 40% of PD patients use some form of complementary therapy to treat their illness, and they frequently do not inform their physicians about such treatments.[1] Furthermore, physicians are often unaware of the types of such therapies that are available to patients, including their potential value and risks. Because of the widespread use and interest in complementary therapies among PD patients, we reviewed those that are promoted to patients, including rationale, mechanisms, potential side effects, and existing evidence of possible efficacy.

Methods

We used the Internet to compile a list of currently promoted complementary therapies for PD. In order to collect information about treatment options promoted directly to patients, we employed the same search methods used by typical patients, including Google searches and reading patient blogs. Search

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Keywords: Parkinson's disease, alternative therapy, complementary therapy, integrative medicine, vitamins, diet, nutrition, exercise, acupuncture, meditation, physical treatments.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 17 November 2014; revised 27 February 2015; accepted 2 March 2015.
Published online 29 June 2015 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12170

doi:10.1002/mdc3.12170

words for PD included the following: treatment, therapy, alternative therapies, complementary therapies, nontraditional therapies, integrative therapies, supplements. For the treatments identified, we then performed a Medline literature search for the period 1980 to 2014 to examine information regarding scientific rationale, neurobiological mechanisms, risks, and possible efficacy.

Results

Lifestyle Changes

Dietary Modifications

Levodopa-Containing Supplements. Fava beans (*Mucuna pruriens*) have been used in traditional Ayurvedic medicine for treating various medical conditions, and levodopa has been isolated from its seeds. Studies have confirmed the presence of measurable, clinically active plasma L-dopa levels subsequent to fava bean ingestion.[2,3] An investigation using an animal model of PD identified antioxidant properties of *M. pruriens*, including the scavenging of reactive oxygen species and iron-chelating activity, suggesting a potential neuroprotective role.[4] There is no clear advantage of using this natural product compared to commercially available L-dopa preparations.

Protein Modification Diets. As PD progresses, most patients develop an unstable response to L-dopa, including motor fluctuations (dyskinesias and wearing off) and dose failures. It has been shown that large meals, especially those with high protein content, can delay gastric emptying of L-dopa, thereby contributing to unstable responses, especially dose failures.[5] Furthermore, amino acids derived from dietary protein can compete with L-dopa for active transport across the intestine and the blood–brain barrier. The end result of these processes is fluctuating delivery of the drug to the brain. Certain diets have been proposed to prevent impaired absorption, such as eating primarily raw vegetables or fruit, but there are little data to support them and they potentially put patients at risk for malnutrition. Protein modification diets have shown some evidence of improving L-dopa pharmacokinetics and helping reduce response fluctuations.

The low-protein diet purports restricting the total daily intake of proteins to less than 0.8 g per kilogram of ideal weight.[6] Small amounts of protein intake do not appear to alter L-dopa pharmacokinetics, but evidence to support the low-protein diet effect on motor fluctuations is lacking.[6] With the protein redistribution diet (PRD), protein intake is reduced at breakfast and lunch with no restriction at dinner. A published double-blind study found that the use of commercially prepared low-protein products was useful in achieving protein redistribution and improving motor fluctuations.[6] Treatment guidelines from the American Academy of Neurology suggest that PRD can be safely recommended in order to improve motor function and motor fluctuations in patients receiving L-dopa.[7] However, complications of PRD have been described, including worsening dyskinesias, weight loss, and malnutrition.[6]

Mediterranean Diet. The Mediterranean diet is modeled on the diet of populations living along the Mediterranean Sea, including the frequent intake of olive oil, nuts, and fish, and has been reported to enhance health status. One meta-analysis of 12 prospective cohort studies involving more than 1.5 million individuals followed for 3 to 18 years found an overall 13% reduction in the incidence of PD among those individuals who adhered to this type of diet.[8] There are no data indicating whether or not the Mediterranean diet conveys any advantages once an individual is diagnosed with PD.

Coffee and Nicotine

Caffeine/Coffee. Although published studies have identified coffee consumption as a negative risk factor for the later development of PD[9] and increasing coffee consumption has been recommended for patients with PD, there is no evidence to support this practice once PD has developed.

Nicotine. Cigarette smoking has consistently been shown to be a negative risk factor for the later development of PD, and an animal model suggests that nicotine may act as an antioxidant or prevent excitotoxicity.[10] There is no available evidence to indicate that smoking or the use of nicotine in other forms is beneficial once PD has appeared.

Exercise

The role of exercise in PD therapy has gained increasing attention and the relevant literature has grown quickly. A complete review of this topic is beyond the scope of this article, so we will summarize the topic. Several studies have shown that aerobic and resistance exercise can improve features of PD.[11] Some research indicates that forced exercise, when an individual is pushed to maintain a faster speed of exercise (e.g., bicycling and treadmill running) than that which is naturally comfortable, may be most helpful, perhaps by altering central control processes.[12,13] Noncontact boxing, an activity that incorporates rapid shifts and adjustments in direction, posture, and weight, has shown evidence of improving gait, balance, and other outcomes.[14]

There has also been recent interest in the possible neuroprotective effects of exercise in PD, potentially through its actions in promoting neuroplasticity. Studies in animals have consistently identified a protective effect of exercise in neurotoxin-induced models of PD. Exercise is believed to exert its neuroprotective actions in animals, at least in part, by increasing neurotrophic factors, such as glial-cell-line–derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF). The mechanisms by which exercise increases neurotrophic factors and the exact mechanisms by which these factors prevent neurotoxic damage are not known. However, each of the

doi:10.1002/mdc3.12170

neurotrophic factors is known to activate multiple signaling cascades. Other neurobiological effects of exercise have been proposed as underlying its potential beneficial effects in PD, including by increasing cerebral blood flow, reducing inflammation, and inhibiting apoptosis. In a review, Petzinger et al. described studies indicating that exercise results in changes in dopamine handling and neurotransmission, including increased synaptic release, delayed synaptic decay, down-regulation of dopamine transporters, and increased affinity to D2 receptors.[15] Exercise has shown evidence of normalizing corticomotor excitability in PD as assessed by transcranial magnetic stimulation. Some epidemiological studies have identified exercise as a protective risk factor for PD, whereas others have not. Behavioral manifestations of PD may also improve with exercise, specifically forced exercise. A review and meta-analysis concluded that a large body of empirical evidence suggests that exercise programs may be an effective strategy to delay or reverse functional decline for people with PD.[16] The meta-analysis included 14 controlled, clinical trials, concluding that exercise is beneficial with regard to physical functioning, health-related quality of life, strength, balance, and gait speed for people with PD, but cautioned that good-quality research is needed. Although it has been suggested that vigorous exercise may have a disease-modifying effect in PD,[17] no published trial of exercise in PD to date has focused on its potential neuroprotective role in slowing the progression of illness. Overall, growing evidence suggests that regular exercise is an important, beneficial activity for patients with PD.

Mindfulness

Mindfulness approaches, such as meditation, have gained interest for patients with PD. Not only are these techniques easily accessible and low in cost, but also there have been growing research findings to suggest a role in strengthening coping skills and improving cognition, memory, and attention in general.[18] Patients with PD also commonly report that meditation has helped motor symptoms, especially tremor, as well as mood, anxiety, and quality of life. To date, however, formal assessments of potential benefits have not been published. Given the low cost and risk, mindfulness is a reasonable addition to the care of patients with PD pending the results of research testing.

Antioxidants as Nutritional Supplements

Oxidative stress, including oxidative damage by free radicals, mitochondrial dysfunction, and the accumulation of oxidized aggregated proteins, has been hypothesized to be a contributor to the pathogenesis of neurodegeneration in PD.[10] This hypothesis has given rise to the notion that there may be a deficiency of protective antioxidants in the brain and/or that dietary antioxidant supplementation may be beneficial in PD.[19] A variety of antioxidant supplements are being publicized for use in PD. The oxidative stress hypothesis contributed to the rationale for the published clinical trials of vitamin E, selegeline, rasagiline, and coenzyme Q10 as potential neuroprotective agents, all of which produced inconclusive results.

Vitamins

Beta-Carotene. Beta-carotene is a precursor to vitamin A that is commonly found in foods such as carrots, pumpkins, sweet potatoes, mangoes, and papayas. Beta-carotene has antioxidant properties, and some evidence from epidemiological studies has been presented that it decreases the risk for PD.[20] Beta-carotene may work by inhibiting lipid peroxidation (LPO) in the brain. Chronic high-dose beta-carotene intake can cause orange tinting of the skin, lower the efficacy of cholesterol-lowering medications, and increase hepatotoxicity of alcohol. High chronic doses have been associated with increased rates of lung cancer, prostate cancer, intracerebral hemorrhage, and overall mortality in smokers. There is no current evidence that beta-carotene is beneficial for patients with PD.

Vitamin B3 (Niacin). Beer and coffee have high levels of niacin and intake of these beverages has been inversely associated with the development of PD.[20] Niacin is biosynthetically converted to nicotinamide adenine dinucleotide (NAD^+), a coenzyme in redox reactions. It has been reported that PD is associated with enhanced breakdown of NAD^+ and suboptimal functioning of certain enzymes requiring niacin as a cofactor.[21] The efficiency of niacin synthesis from tryptophan varies among different individuals, but this process has not been studied in patients with PD. Doses of 50 mg or more of niacin can cause "niacin flush," a burning or tingling sensation in the face and chest and red or flushed skin. Currently, there is insufficient evidence to recommend niacin for routine use in patients with PD.

Vitamin B6 (Pyridoxine). Higher intake of vitamin B6 was associated with a significantly decreased dose-dependent risk of PD.[22] Vitamin B6 itself has antioxidant properties. In addition, it is required for the conversion of homocyteine to cysteine, which is the rate-limiting step in the synthesis of the antioxidant, glutathione. The major side effect of excessive vitamin B6 intake is neuropathy. Vitamin B6 has not been adequately studied in patients with PD to recommend its use.

Vitamin C. No clear effects of vitamin C intake on the risk of PD were found in some studies, whereas one did identify an inverse relationship between PD and vitamin C use. Vitamin C may exert neuroprotective actions through its modulation of excitatory amino acid activity.[23] Large doses of vitamin C can increase the chance of getting kidney stones. It can also worsen blood iron disorders resulting from the increase of iron absorption. Vitamin C might worsen sickle cell disease and the condition glucose-6-phosphate dehydrogenase deficiency, in which it can induce hemolysis. The most common side effects of vitamin C ingestion are nausea, vomiting, heartburn, abdominal cramping, and headaches. There is insufficient evidence to recommend its use in PD.

doi:10.1002/mdc3.12170

Vitamin D. Vitamin D functions as a secosteroid hormone, which acts on many biological targets owing to the presence of the vitamin D receptors that are present on many cell types, including neurons and glia. Vitamin D is generated from ultraviolet B radiation and from dietary intake. Recently, there has been increasing epidemiological evidence of a link between vitamin D deficiency and PD. A high concentration of vitamin D receptors has been found in the substantia nigra (SN), suggesting the possibility that low receptor or vitamin levels might contribute to loss of dopaminergic neurons in this region and development of PD.

Vitamin D may provide neuroprotective benefits for patients with PD. In both 6-hydroxydopamine and MPTP animal models, administration of 1,25-dihydroxy-vitamin D led to a reduction in dopaminergic neuronal death, whereas it increased GDNF, BDNF, and glutathione levels.[24] There is also evidence that vitamin D reduces expression of proinflammatory cytokines. Vitamin D has been hypothesized to exert neuroprotective effects through a combination of calcium-mediated and antioxidative mechanisms, detoxification, increased nerve conduction, and immunomodulation.[24] Recent studies involving the general population have identified a relationship between vitamin D deficiency and reduced cognitive functioning, but other research has not confirmed these findings. Studies are needed to evaluate whether vitamin D supplementation can protect against cognitive impairment among those with PD.[25] There currently is insufficient evidence to support routine supplementation with vitamin D in patients with PD.

Vitamin E. Most studies have found no association between vitamin E intake and risk of PD. However, one study found that the use of cod liver oil, a vitamin E supplement, was associated with a reduced risk of PD.[20] Another study reported a dose-dependent relationship between vitamin E intake and risk reduction for PD.[19] In support of a potential neuroprotective effect, it has been shown, in an animal model, that high levels of fat-soluble antioxidants, such as vitamin E, can reduce LPO in the SN.[19] A multicenter, randomized, double-blind, placebo-controlled trial, known as the DATATOP trial, failed to identify any neuroprotective effects of vitamin E.[26]

Herbs and Botanicals

Flavonoids. Flavonoids act to limit oxidative stress, and the flavonoid of greatest interest for PD has been melatonin. Melatonin (*N*-acetyl-5-methoxy-tryptamine) is an indoleamine derived from tryptophan and is produced in the pineal gland. In addition to its role in the sleep-wake cycle, melatonin is an endogenous antioxidant. By interacting with reactive species, melatonin is metabolized to several metabolites that are effective free radical scavengers, and melatonin enhances expression of genes that code for antioxidative enzymes. Research has demonstrated melatonin's protective properties against oxidative damage to lipids, mitochondrial and nuclear DNA, and proteins. Melatonin has been found to prevent pro-oxidative effects of dopamine and L-dopa in vitro, and a number of studies have identified neuroprotective properties of melatonin in animal models of PD.[27] Overall, melatonin has demonstrated promising antioxidant and neuroprotective effects, is well tolerated, and appears to be a promising agent for further study. At this time, however, there is insufficient evidence to recommend its use for these purposes. Of note, a benefit of melatonin (3–12 mg at bedtime) has been reported for patients with PD with associated rapid eye movement sleep behavior disorder.[23]

Resveratrol is another flavonoid antioxidant that is present in many vegetables, fruits, grains, roots, flowers, seeds, and, particularly, red wine. Resveratrol has been reported to increase the level and function of manganese-superoxide dismutase,[28] which has been shown to promote resistance to oxidative stress in mitochondria and to have antiapoptotic effects. Resveratrol is under investigation as a potential brain neuroprotective agent related to aging, metabolic toxin exposures, and neurodegenerative diseases, including PD.[28] This compound appears to mimic caloric restriction, an intervention with evidence of combating the aging process, by increasing the activity of the SIRT1 gene, which codes for the protein, sirtuin 1. Sirtuin 1 deacetylates a number of proteins that are involved in metabolism, apoptosis, and cellular defenses. Resveratrol appears to be a compound of interest for PD, but insufficient evidence of its benefits exists at this time. Patients taking resveratrol should be aware that it can interact with anticoagulants, such as aspirin, warfarin, or clopidogrel, to prolong bleeding and can exhibit mild estrogenic activity, which can be of concern to pregnant and breastfeeding women and those with certain cancers or other estrogen-sensitive conditions.

Gastrodin. The plant *Gastrodia elata* has been used medicinally to improve headaches, dizziness, vertigo, and convulsive disorders. A prominent component of the plant is the phenolic glucoside, gastrodin. Gastrodin regulates levels of neurotoxic proinflammatory mediators, reduces LPO, possesses antioxidant properties, and scavenges free radicals. Neuroprotective effects of gastrodin were observed in both cell and mouse models of PD,[29,30] suggesting that gastrodin may be a good candidate for further study as a potential neuroprotective agent in the illness. However, it cannot currently be recommended owing to insufficient evidence. Reported side effects of gastrodin are headache and dry mouth.

Green Tea Phenols. Green tea polyphenols are being considered as potential therapeutic agents for PD patients. One study found a moderate PD risk reduction for tea consumers, compared to nontea drinkers. Green tea is said to have biological effects that might benefit PD, including antioxidant actions, free radical scavenging effects, iron-chelating properties, and cell survival/cell cycle gene modulation. Further studies are needed to determine the value of green tea polyphenols for PD.[31]

Ginkgo biloba. Ginkgo biloba is a tree native to China. Whereas ginkgo biloba is best known as a supplement used to treat memory loss in patients with Alzheimer's disease, it has been

doi:10.1002/mdc3.12170

studied in relationship to PD because of its antioxidative properties. Studies have shown evidence of antioxidant and -apoptotic neuroprotective properties of ginkgo biloba in the 6-hydroxydopamine rat model, as well as inhibition of monoamine oxidase (MAO) activity.[32] There are side effects associated with ginkgo biloba, especially interactions with anti-platelet and -coagulant medications (i.e., aspirin and warfarin). Individuals taking antidepressants may experience side effects because of gingko's action of inhibiting MAO. Other side effects of gingko include gastrointestinal discomfort, nausea, diarrhea, headaches, palpitations, and restlessness. There is insufficient evidence to recommend the use of ginkgo biloba in patients with PD.

Milk Thistle. The consumption of milk thistle, a flowering herb, has gained popularity among PD patients. Although there are no published studies exploring the effects of milk thistle on PD, one in vitro study demonstrated that milk thistle extract can promote neuronal differentiation and survival.[33] Specifically, silymarian, the main component of milk thistle extract and a complex mixture of polyphenolic compounds, has been shown to decrease oxidative stress and protect cells against apoptosis.[34] Of potential relevance, milk thistle is thought to improve liver function by removing toxins and helping to repair damaged liver cells. Some have recommended the use of milk thistle by PD patients to strengthen the liver, recognizing that most anti-parkinsonian medications are hepatically metabolized. At this time, however, there is insufficient evidence to support its consumption by patients with PD.[33]

Other Dietary Supplements

Acetyl-L-Carnitine and Alpha-Lipoic Acid. Acetyl-L-carnitine is involved in mitochondrial energy metabolism and has strong antioxidant effects. It has been shown to have neuroprotective actions in models of brain ischemia, peripheral nerve injury, and spinal cord injury, and it has been suggested as a possibly useful antioxidant in PD. Alpha-lipoic acid is a cofactor for some mitochondrial enzymes and functions as an antioxidant in the brain. In an animal model study that used the nigrotoxin, rotenone, neuroprotective effects were observed after delivery of a combination of both acetyl-L-carnitine and alpha-lipoic acid.[35] There have been no studies in patients with PD. Use of alpha-lipoic acid supplements has been associated with headache, paresthesias, skin rash, muscle cramps, and hypoglycemia. It cannot yet be recommended for use in patients with PD.

Coenzyme Q10. MPTP has been shown to induce parkinsonism in primates by inhibiting complex I in the mitochondrial electron transport chain, and in patients with PD, there is reduced complex I activity in the SN and in platelets. Thus, it is likely that impaired complex I activity plays an important role in the pathogenesis of PD.[36] It is believed that coenzyme Q10 is the electron acceptor for mitochondrial complexes I and II and that it can improve complex I activity and reduced levels of coenzyme Q10 have been identified in the mitochondria of patients with PD.[37] A phase III trial of coenzyme Q10 was halted prematurely because of demonstrated futility in being able to demonstrate protective effects.[38] At this time, coenzyme Q10 cannot be recommended as an efficacious supplement for patients with PD.

Fish Oil. There is some evidence that the omega-3 fatty acids present in fish oil reduce proinflammatory cytokine production and may reduce inflammation in PD. However, there is no evidence that fish oil improves the symptoms of PD or slows progression. Up to 3 g of fish oil per day is considered safe, but fish oil and omega-3 fatty acids can cause a number of gastrointestinal and neurological side effects and can raise blood pressure.

Glutathione. Glutathione is a powerful antioxidant found naturally in the body with levels that decline with age, and reduced levels of glutathione have been found in dopaminergic neurons of PD patients.[39] Though small open-label studies have reported a benefit of glutathione for PD, a randomized, placebo-controlled, double-blinded trial of intravenous glutathione in 20 patients with PD showed no evident efficacy.[40] At this time, there is insufficient evidence to support the use of glutathione in PD.

Selenium. Selenium is a nonmetal chemical element that is an essential micronutrient. It is a cofactor for antioxidant enzymes glutathione peroxidase and thioredoxin reductase and functions as an antioxidant in the brain. In a study of rats with 6-hydroxydopamine lesions, selenium was found to reduce dopamine loss and increase measured antioxidant levels.[41] No studies of selenium in patients with PD have been published. Selenium is toxic if taken in excess, and it has been advised that an amount of 400 μg per day should not be exceeded.

Iron and Chelation Therapy

Iron participates in free radical formation and induction of LPO. Iron levels are selectively increased in the SNc of patients with PD, but whether or not iron participates in the process of neurodegeneration remains unclear. One study found that a diet rich in iron was associated with a 30% increase in risk of PD in both men and women.[42] Studies investigating the relationship of serum iron levels to risk of PD have produced conflicting results.

Chelation works by bonding a chelating agent, such as ethylenediamine tetra-acetic acid (EDTA), with a metal and rendering it inactive. Chelation therapy has been used successfully for diseases with metal overload, such as hemochromatosis, and it is widely publicized for use in PD. In studies done in MPTP animal models, a reduction of iron in the brain seemed to be well tolerated.[43] However, there have been no conclusive studies done on humans regarding the value of iron chelation for PD. Chelation is expensive and has several known potential risks, including embryotoxicity, teratogenicity, arthritis, severe neutropenia, and agranulocytosis. Because there is no proven benefit in PD, chelation therapy cannot be recommended.

doi:10.1002/mdc3.12170

Cannabis

There has been interest in cannabis as a treatment option for PD. Anecdotally, some patients have reported that it alleviates motor and nonmotor symptoms, particularly PD-related pain and sleep problems. Canniboid receptors are highly expressed in the brain, particularly in the basal ganglia. It is currently believed that Δ9-tetrahydrocannabinol (THC), the psychoactive ingredient of cannabis, might be responsible for the benefit reported by PD patients and might exert neuroprotective effects. THC binds to cannabinoid receptors in the endocannabinoid system in order to activate G proteins that then activate or inhibit a number of signal transduction pathways involved in cognition, mood, motor control, feeding behaviors, and pain.[44]

In a small subject sample, Lotan et al. assessed the clinical effects of smoking cannabis on PD and found an overall improvement in motor symptoms, including tremor, rigidity, and bradykinesia, and in pain severity. Bad taste and drowsiness were the main side effects described.[45] Other studies of cannabis in PD have generally involved small samples and reported quite disparate results, ranging from strong benefits to none. There are medical and societal concerns about medical marijuana that have included potential side effects such as adverse effects on driving, its potential to increase the risk for dementia, and its reputation as a possible "gateway" drug to more addictive substances. Larger studies using standard clinical trials methodology are needed to determine the possible efficacy of cannabis for PD.[44]

Physical Treatments

Tai Chi

Tai chi, which includes rhythmic weight shifting, symmetric foot stepping, and consistent movements aimed at improving stability, has been shown to improve balance, reduce falling rates, increase gait velocity, and decrease bradykinesia.[46] Tai chi may be a useful activity for patients with PD, particularly those with balance problems.

Dance Therapy

Dance therapy has been proposed as a physical intervention for patients with PD. Different types of dance have been shown to improve gait, mobility, balance, and cognitive function.[47] Dance therapy may be helpful psychologically for patients with PD given its social nature and represents an activity that patients and their care partners can perform together.

Music Therapy

In a 3-month study, 32 PD patients attended weekly classes of music therapy, consisting of choral singing, voice exercises, and rhythmic and free body movement, combined with physical therapy.[48] This combination therapy was found to improve bradykinesia and mood. More work in assessing the effects of music therapy in PD is needed.

Light Therapy

Light therapy has been proposed as a treatment for PD. It is in use to treat seasonal depression and sleep disturbances and is thought to work by suppressing release of melatonin. Paus et al. studied bright-light therapy given for 15 days in the morning for 30 minutes each day in patients with PD.[49] It was hypothesized that light therapy would stabilize the circadian release of melatonin and improve monoaminergic function. The study showed significant improvement in UPDRS scores as well as improvement in the Beck Depression Inventory, especially for those patients that had reported disturbance of mood. Additional research is needed to confirm the results of this preliminary study.

Whole Body Vibration

Whole body vibration using a vibrating exercise machine has been proposed as another complementary treatment for PD. Machines are on sale for up to $14,000 each. One randomized crossover study involving 68 patients with PD found a 16.8% improvement in UPDRS scores, with tremor and rigidity responding best.[50] On the other hand, two other studies, one being a double-blind, sham-controlled trial, found no evidence of efficacy.[51,52] This form of therapy cannot be recommended at this time.

Acupuncture

Acupuncture is often discussed as a complementary treatment for PD. In a study using the unilateral 6-hydroxydopamine-lesioned rat model, acupuncture was observed to cause an increase in tropomyosin receptor kinase B (trkB)-positive cells in the nonlesioned side of the SN. trkB is a component of BDNF. The study hypothesized that, through this action, acupuncture could have neuroprotective effects in the brain.[53] Two double-blinded studies involving PD patients, however, found no clear evidence of efficacy for acupuncture.[54,55] In all, there is insufficient evidence to support the use of acupuncture in patients with PD.

Discussion/Conclusions

As reviewed above, a large number of lifestyle, dietary, and nutritional and physical treatments are routinely being promoted on the Internet to patients with PD as being beneficial for their illness. Fortunately, most have fairly few and relatively mild potential risks and side effects. In many cases, the treatments are linked to reasonable justifications based on their mechanism of action and current theories on causes of neurodegeneration in PD. Some of these treatments have evidence of neuroprotective properties in animal models of PD. Use of others has been associated with a decreased risk of developing PD. But few have

doi:10.1002/mdc3.12170

documented evidence of benefit in patients who already have PD. In particular, randomized, controlled, and blinded studies are lacking. Despite this, many of these treatments are provided at a substantial expense to patients and their families.

Chelation therapy is associated with substantial costs and serious risks and has no evidence of benefit, and this treatment should be avoided. Similarly, intravenous therapies, such as with glutathione, can be expensive and are lacking evidence of any benefits. These, too, should not be used. The protein redistribution diet is considered safe and effective for improving motor function and motor fluctuations in some patients with PD. Some of the other treatments have interesting preliminary evidence of potential benefit, either for lessening symptoms or providing possible neuroprotective actions, but, in all cases, more research to establish efficacy is needed. Treatments that fall into this category would include some of the antioxidative or -inflammatory supplements, such as melatonin, resveratrol, acetyl-L-carnitine, alpha-lipoic acid, gastrodin, vitamin D, green tea phenols, and milk thistle. Current evidence, although preliminary, supports the use of aerobic exercise, meditation, Tai chi, and dance and music therapy in patients with PD. Exercise is of particular interest because potential neuroprotective actions are coming to light. Current clinical studies of complementary medicine therapies for PD that are registered on ClinicalTrials.gov are shown in Table 1.

In conclusion, patients with PD are faced with many recommendations for complementary therapies. Physicians should know about these in order to have informed discussions with their patients. Some deserve further study.

TABLE 1 Current complementary therapy trials from ClinicalTrials.gov

	Area of Inquiry	ClinicalTrials.gov Identifier
Lifestyle changes	Dietary modifications	NCT02275884 (chocolate)
	Coffee and nicotine	NCT01738178 (caffeine) NCT01216904 (nicotine) NCT01560754 (nicotine)
	Exercise	NCT01506479 NCT02175082 (cycling) NCT02267785 NCT01156714 NCT01768832 NCT01636297 (cycling) NCT02230267 NCT01749917 NCT02231073
	Mindfulness	NCT01607697
	Antioxidants as nutritional supplements	NCT01563913 (omega-3 FAs) NCT01470027 (*N*-acetylcysteine) NCT01324426 (glutathione)
	Cannabis	NCT02028858
Physical treatments	Dance therapy	NCT01939717
	Light therapy	NCT02175472 NCT02072642
	Whole body vibration	NCT02306863
	Acupuncture	NCT01970813
General	Complementary and alternative treatments	NCT02194816

FAs, fatty acids.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

M.L.R.: 1A, 3B
C.S.-H.: 1C, 3A
E.H.: 1C, 3A
A.R.: 1C, 3A
B.T.: 1C, 3A
T.D.: 1C, 3A
M.C.E.: 3B
R.K.: 1A, 3B

Disclosures

Funding Sources and Conflicts of Interest: The authors report no sources of funding and no conflicts of interest.

Financial Disclosures for previous 12 months: M.L.R. served on the speakers bureau for Teva and Allergan and received research support from Ipsen. R.K. served on the speakers bureau for Teva and received research support from NIH, Astra-Zeneca, Otsuka, Phytopharm, and Psyadon.

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