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REVIEW ARTICLE

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by resting tremor, rigidity, and bradykinesia. The pathological processes begin years/decades before the first motor symptoms are observed. The prevalence of PD increases with age, and a global burden of PD is expected in coming decades. A recent study estimated that by 2030, there may well be more than 2 million patients with PD in the European Union and the United States [1].

PD is one of the few neurodegenerative disorders for which highly effective symptomatic therapies have been available for decades. Although levodopa is considered the most potent for efficacy (gold standard), its use is associated with motor complications including wearing off, dyskinesia, and on−off phenomenon. Evidence from preclinical studies suggests that these complications are related to pulsatile stimulation of the striatal dopamine receptors due to multiple orally administered levodopa intake. Dopamine agonists provide more stable plasma levels and therefore more stable receptor stimulation, but they fail to reach the efficacy of levodopa. Despite recent progress in the symptomatic treatment of PD, there are numerous aspects that have not been adequately addressed [2]. These include the prevention of motor complications, the question of neuroprotection, postural instability, cognitive dysfunction, freezing, gait disturbances, and others. In animal studies, a substantial number of drugs have proved effective either in preventing neurodegeneration or in producing symptomatic benefit. However, in the subsequent human clinical trials, many of them failed to produce the same efficacy as seen in preclinical studies. These failures are not necessarily an indication of drug failure or drug action but may be related to inadequate administration, misjudged clinical endpoints, study duration, and poor trial design. Besides the dopaminergic deficit, alterations in other neurotransmitter systems in the brain of patients with PD have been clearly demonstrated, including the noradrenergic, serotoninergic, glutamate, adenosine, noradrenaline, and 5-hydroxytryptamine systems. These so called nondopaminergic drugs offer new therapeutic options for complications where dopaminergic drugs have already failed.

We made use of the www.clinicaltrials.gov database to summarize some of the pharmacological compounds being investigated in clinical trials relating to the motor symptoms of PD. Due to space limitations, we are unable to discuss the numerous compounds already in clinical trials that do not address motor symptoms or complications.

Nicotine

Epidemiological studies have consistently indicated that smoking can delay the onset of PD symptoms [3], suggesting that smoke may contain compounds that are potentially neuroprotective. This observation is supported by experimental studies showing a protective effect of nicotine against neurotoxic insults [4]. It has recently been demonstrated that nicotine and hydroquinone inhibit alpha synuclein aggregation, indicating a protective action against nigrostriatal damage [5]. Moreover, a variable and moderate symptomatic effect of nicotine has also been revealed. In a pilot open-label trial involving a small group of six patients,

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nicotine administration improved motor symptoms [6], whereas in larger randomized, double-blind trials with 16 and 32 patients, it was ineffective [7, 8]. On the other hand, recent data on primates showed that nicotine can attenuate levodopa-induced dyskinesias [9]. Taken together, these observations suggest that nicotine or nicotinic receptor ligands may be beneficial to patients with PD by slowing disease progression, improving motor symptoms, and decreasing levodopa-induced dyskinesias [10]. To prove this hypothesis and to clarify the previous contradictory data, a phase II, randomized, open-label, efficacy study (NICOPARK2) of transdermal nicotine administration is under way.

Inosine

The natural antioxidant urate has been proposed as a predictor of both risk and progression of PD. The neuroprotective effect of antioxidants has been well demonstrated in animal models of PD [11]. In a retrospective analysis of the patients who participated in the DATATOP [12] and PRECEPT [13] trials, those with baseline serum urate levels in the upper normal range displayed a 40% slower rate of clinical progression compared with those with a lower baseline level. Similarly, the dopamine transporter (DAT) single photon emission computed tomography (SPECT) indicated a lower rate of loss of striatal DAT in patients with higher baseline urate levels. This association was verified in a large PRECEPT prospective clinical trial on 804 patients with early PD. Oral administration of the blood-brain-barrier-penetrant urate precursor inosine can readily elevate the serum urate level, and its effect will be studied in patients in a phase II clinical trial (SURE-PD) designed to clarify the safety of urate elevation.

Creatine

Creatine (CRT) exerts neuroprotective effects in vivo against various neurotoxins and in transgenic mouse models of both amyotrophic lateral sclerosis (ALS) and Huntington's disease [14–16]. The mitochondrial dysfunction and energy deficit have been well demonstrated in all neurodegenerative disorders, including PD. CRT acts in the mitochondria; its administration increases brain concentrations of both CRT and phosphocreatine (PCr) and it interacts with the mitochondrial isoform of creatine kinase (Mi-CK) to inhibit the mitochondrial transient pore. Neuroprotection against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been demonstrated in mice deficient in Mi-CK, which suggests that the neuroprotective effects of creatine are not mediated by an effect on this kinase to inhibit the transient pore but by and PCr, thereby buffering the energy deficit [17]. Several clinical trials have been conducted in different disorders without providing a robust clinical benefit, including a randomized double-blind, placebo-controlled trial on 104 patients with ALS [18], a 2-year open-label pilot study on 13 Huntington's disease patients [19], and a randomized, double-blind phase II trial of CRT in early PD [20]. A phase III, long-term (5-year follow-up), multicenter, double-blind, placebo-controlled study of PD is ongoing (NET-PD LS1).

Folic acid

Folate is an essential vitamin that participates in many essential cell functions. Folate deficiency is related with an increased level of homocysteinemia, which is characteristic of PD. In some patients, an antibody is produced against folate that prevents it from properly entering the brain and could worsen certain symptoms of PD, such as cognitive function [21]. A study is being conducted to assess the impact of folate on the progression of PD. Although epidemiological data suggest an inverse association between the folate status and colorectal tumors, it is important to point out that recent folate trials have raised concern about the potential association with a higher risk of cardiovascular disease and some forms of cancer [22].

Fipamezole

Previous studies with the MPTP nonhuman primate model of PD [2] have demonstrated that alpha adrenergic receptor antagonists such as fipamezole can attenuate levodopa-induced dyskinesia [23]. Unfortunately, data from these studies were not always consistent and could not be translated into a direct clinically significant benefit. A well-designed, phase II, randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of fipamezole in the treatment of levodopa-induced dyskinesia in advanced PD is recruiting patients.

Vitamin D

Retrospective observations suggest that an inadequate vitamin D intake, particularly in the elderly, may be a significant factor in the pathogenesis of PD [24]. A retrospective systemic analysis of stored samples in a clinical research database indicated that vitamin D deficiency occurs in the majority of patients with PD (55%), more frequently than in internal medicine clinics (36%) [25]. Moreover, low vitamin D levels have been associated

with slower walking speeds, poorer memory and thinking, and depression. A phase IV, randomized, double-blind, active-control, efficacy study is now being conducted to evaluate the effects of a high-dose of vitamin D supplementation (54,200 IU/week) on the clinical symptoms of PD (VIDIP PILOT).

Coenzyme Q10 (CoQ10)

The major steps in the pathophysiology of PD are cellular energy depletion and consequent oxidative stress, leading to a cellular dysfunction and cell death. CoQ10 is an electron acceptor bridging mitochondrial complexes I and II/III and a potent antioxidant that partially recovers the function of neurones. In a previous phase II, multicenter, randomized, parallel-group, placebo-controlled, double-blind, dosage-ranging clinical trial, it was demonstrated that CoQ10 at dosages of 300, 600, and 1,200 mg/day was safe and well-tolerated in 80 patients with early, untreated PD. The data also indicated that CoQ10 may slow the progression of PD, as measured by the Unified Rating Scale (UPDRS) [26, 27]. A randomized, placebo-controlled, phase III trial of two doses (1,200 and 2,400 mg/day) of CoQ10 has been initiated to confirm and extend the results of the earlier phase II study in early PD (QE3). This study will also evaluate independent function, cognition, and quality of life.

Levetiracetam (LEV)

Levetiracetam is a widely used antiepileptic drug, which can also be administered to treat chronic pain. Its mechanism of action is complex: it has an indirect effect on the gamma aminobutyric acid (GABAergic) system, modulates ionic currents, influences expression of several genes, and binds to the synaptic vesicle protein 2a. In an open-label, small study involving only nine PD patients with moderate to severe levodopa-induced dyskinesia, LEV was not well tolerated, resulting in deterioration and worsening of some PD symptoms, intolerable somnolence, and worsening of dyskinesia in most patients. The dose was titrated up to a high level (3,000 mg/day) [28]. In another small, open-label, pilot study also involving only nine PD patients who experienced peak-dose dyskinesia, LEV significantly improved the ‘on time’ without dyskinesia or with nontroublesome dyskinesia. In this case, the mean dose was lower (625 ± 277 mg/day) [29]. A multicenter, randomized, double-blind, placebo-controlled trial (LeLe-Dys) has been designed to determine the efficacy and safety of levetiracetam on levodopa-induced dyskinesias in advanced PD.

SYN 115

Adenosine serves as a signaling molecule in the central nervous system. One of its receptors, the adenosine A (2A) receptor, is localized to the basal ganglia and modifies the indirect output pathway. A(2A) antagonists can modulate the output of the striatum, which is believed to be critical for the occurrence of motor complications of PD, and they have been shown to be associated with an improved motor function in animal models of PD. SYN 115, a potent and selective inhibitor of the A(2A) receptor, modulates the production of dopamine, glutamine, and serotonin in specific regions of the brain. In preclinical models of PD and in clinical trials with other A(2A) antagonists, the inhibition has resulted in increased levels of dopamine and improved motor deficits [30]. To prove its efficacy, a phase IIa and a phase IIb trial with SYN 115 were initiated in 2009. The efficacy measures are also included in functional magnetic resonance imaging (fMRI) studies.

Safinamide

Safinamide has a novel mode of action, targeting multiple systems, and potentially provides better motor control. This orally administered alpha-aminoamide derivative of milacemide behaves as a monoamine oxidase B (MAOB) and glutamate release inhibitor and blocks voltage-sensitive sodium (Na^{+}) and calcium (Ca^{++}) channels and glutamate release. The high selectivity for the sigma-1 receptor site does not entail psychotomimetic or behavioral changes. In several experimental in vitro and in vivo models, safinamide exerts neurorescuing and neuroprotective effects. In a small pilot study involving 13 PD patients receiving a high dose of safinamide, a symptomatic motor benefit was detected [31]. A phase III, double-blind, placebo-controlled study is ongoing to investigate the efficacy and safety of higher doses of safinamide (50–200 mg/day) as add-on therapy in patients with early PD.

Aplindore

Aplindore is an orally active, small-molecule, partial dopamine agonist. The striatal dopamine D_2 receptor selective profile of aplindore suggests that it should be effective for the treatment of PD. In 2008, a successful phase II efficacy and safety trial was completed in early PD patients [32]. Another randomized, double-blind, placebo-controlled efficacy and safety trial in patients with early PD is being conducted (APLIED).

Methylphenidate (MPH)

The amphetamine derivate methylphenidate stimulates the nervous system and also inhibits catecholamine reuptake, therefore increasing dopamine levels in the brain. It is used to treat patients with attention deficit and hyperactivity disorder. Early observations with MPH suggest that this compound is not useful for ameliorating cognitive and affective symptoms, but in certain cases, it improves attention [33]. The effects of MPH on motor deficits are somewhat controversial. Some small, open, pilot studies demonstrated that a low dose may improve gait, and especially freezing, in patients with severe PD, without the need for exogenous levodopa [33–35]. However, this was not confirmed by other trials [36, 37], including one set up in 2007. In another pilot study, MPH was effective in lowering fatigue scores in patients with PD following a 6-week treatment period [38]. To establish the efficacy of MPH against gait impairment in PD, a randomized, placebo-controlled, double-blind trial was set up in 2007, which is still recruiting patients. Another study is about to start this year (2009), concentrating on gait impairment and attention deficit (PARKGAIT-II).

Isradipine

A substantial body of evidence supports the role of increased level of intracellular Ca^{++} in neurodegeneration. The elevated intracellular Ca^{++} level produces oxidative stress, mitochondrial dysfunction, energy deficit, and excitotoxicity [39]. Administration of isradipine, a blocker of L-type Ca^{++} channels, confers neuroprotection in toxin models of PD, pointing to a potential neuroprotective effect with a drug class that has been used safely in humans for decades. Isradipine-treated animals displayed a dose-dependent reduction in levodopa-induced rotational behavior and abnormal involuntary movements. The involuntary movements were not reduced when isradipine treatment was started concomitantly with levodopa. These results indicate that isradipine, at a therapeutically relevant dose, might be a treatment option for preventing levodopa-induced dyskinesia in PD. [40]. To prove this hypothesis, a phase II safety and tolerability trial was initiated in 2008.

V1512

After decades as treatment for PD, levodopa is still considered the gold standard. V1512 combines levodopa methyl ester, an enhanced soluble pro drug of levodopa, with carbidopa. It is water soluble and available in an effervescent formulation as a potential novel form of treatment for PD. There is evidence that some motor complications, such as delayed onset or lack of effect of levodopa, may be due to erratic drug absorption. This water-soluble, effervescent formulation may overcome some of these complications of levodopa treatment, as indicated in a previous randomized, double-blind, double-dummy study with 78 PD patients [41]. To test the efficacy and safety of V1512, a randomized, double-blind, active-controlled, phase I and II trial is ongoing.

Neu 120

Neu 120 has been developed as adjunct therapy to levodopa in patients with motor fluctuations and in those who do not tolerate optimum doses of levodopa. Neu 120 is a potent and selective noncompetitive N-methyl-D-aspartic acid (NMDA) receptor modulator and also inhibits MAOB and glycogen synthase kinase 3 beta (GSK-3B) in vitro, without significant interaction with other known receptors, transporters, or enzymes. The aims of its administration are to improve motor symptoms and to reduce levodopa-induced dyskinesia. Neu 120 has been tested in many animal models of PD and is entering a randomized, double-blind, placebo-controlled phase IIa trial.

Sch 420814

Antagonism of the A(2A) receptor has opened up a new approach in the treatment of PD. An exploration of pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine A(2A) antagonists led to the clinical candidate Sch 420814 [41], a potent, highly selective competitive antagonist of the human A(2A) receptor. A randomized, single-blind, placebo-controlled, pharmacodynamics study was commenced this year (2009) (Study P05550AM1).

Kynurenine

Kynurenine is an intermediate in the pathway of the tryptophan metabolism, the pathway known to be responsible for nicotinamide adenine dinucleotide (NAD metabolism [43–45]. L-kynurenine, the central agent of this pathway, can be converted to other important compounds: the neuroprotective NMDA antagonist kynurenic acid and the neurotoxic quinolinic acid. Abnormalities have been demonstrated in the kynurenine pathway in PD [46]. This NMDA receptor antagonist reduced levodopa-induced dyskinesias in an animal model, and administration of kynurenine-3-hydroxylase inhibitor delayed the development of levodopa-induced dyskinesias in monkeys [47, 48].

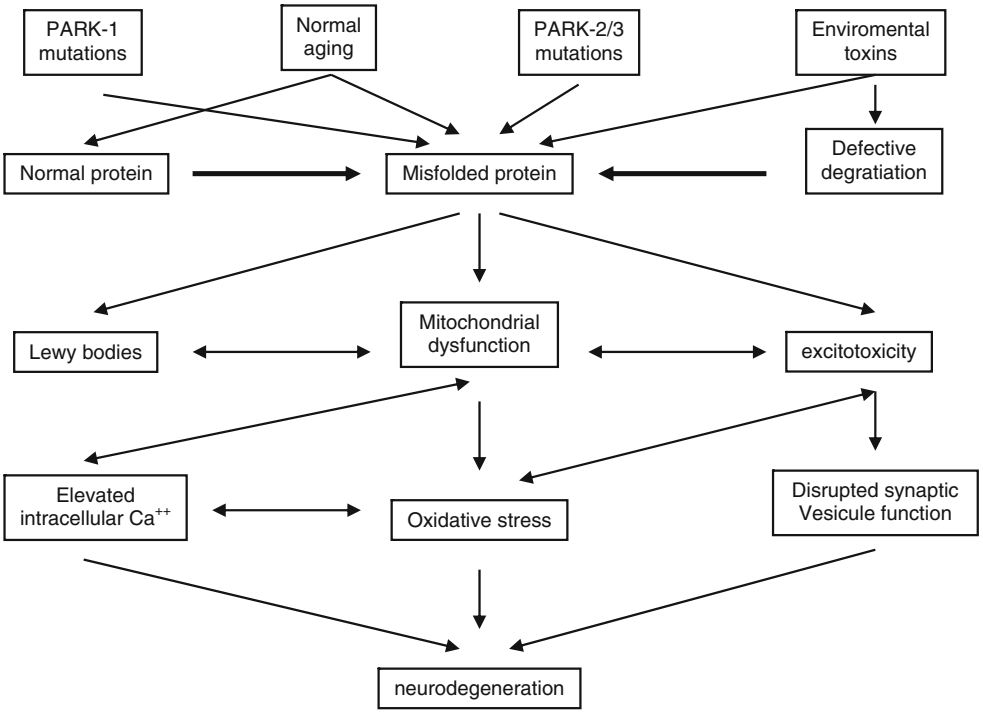

Fig. 1 The putative pathomechanism of Parkinson's disease. Both genetic and environmental factors can initiate a cascade of molecular steps, which lead to excitotoxicity, mitochondrial dysfunction, oxidative stress, and ultimately cell death

Table 1 Some pharmacological compounds now in clinical trials aimed at alleviating motor symptoms of Parkinson's disease (PD)

Drug	Mechanism of action	Effects	Clinical effect
Nicotine	Nicotine receptor agonist	Inhibit alpha-synuclein aggregation	Improve motor symptoms, reduce dyskinesia
Inosine	Antioxidants	Decreased free radical production	Slow progression
Creatine	Acts on mitochondria	Improved energy homeostasis	Slow progression
Folic acid	Essential vitamin	Decreased homocysteine levels	Slow progression
Fipamezole	α_2 adrenergic receptor antagonists	α_2 receptor inhibition	Reduced dyskinesia
Coenzyme Q10	Acts on mitochondria	Improved mitochondrial function	Slow progression
Vitamin D	Vitamin	Unknown in PD	Improved motors symptoms
Levetiracetam	Complex	Complex	Reduced dyskinesia
Syn 115	Adenosine 2A [A(2A)] receptor antagonists	A(2A) receptor inhibition	Improved motor symptoms
Safinamide	MAO-B/ glutamate release and Na^+ and Ca^{++} channels inhibitor	Complex	Improved motor symptoms; slow progression
Aplindore	Partial DA agonists	Dopamine receptor stimulation	Improved motor symptoms
Methylphenidate	Inhibits catecholamine reuptake	Increased dopamine level	Improved gait and attention deficit
Isradipine	L-type Ca^{++} channel blocker	Reduced excitotoxicity; improve mitochondrial function	Reduced dyskinesia
V1512	Levodopa	Dopaminergic stimulation	Improved motor symptoms
Sch 420814	A(2A) receptor antagonists	Decreased receptors activation	Improved motor symptoms; reduce dyskinesia
Neu 120	NMDA modulator MAO-B/GSK-3B inhibitor	Complex	Improved motor symptoms; reduce dyskinesia
Kynurenine	NMDA antagonists	Inhibition of excitotoxicity	Reduced dyskinesia

MAOB Monoamine oxidase B, Na^+ sodium, Ca^{++} calcium, *DA* dopamine agonists, *NMDA* N-methyl-D-aspartic acid, *GSK-3B* glycogen synthase kinase 3 beta

On the bases of these data, a clinical trial with chlorokynurenine is being set up.

Summary

PD is a neurodegenerative disorder triggered by genetic and/or environmental factors and the pathological processes begin many years before motor symptom manifestation (Fig. 1). Several drugs are available to treat PD, but there are still many aspects of the disease that have not been well addressed. These include nonmotor symptoms, disease progression, and preventing levodopa-induced motor complications. Besides the concept of continuous dopaminergic stimulation, the benefit of which has not been proved in clinical settings (see the STRIDE-PD trial), the nondopaminergic drugs offer promising alternatives to dopaminergic medication. However, modification and further development of dopaminergic molecules may provide significant symptomatic improvement and improved quality of life. In this review, we summarized new treatments that are in the pipeline, with patients being recruited for clinical trials. Among the compounds being studied are well-known ones (e.g., folic acid or methylphenidate), which have been used in other diseases, and newly developed drugs with known mode of action (e.g., the dopamine agonist aplindore) or compounds with completely new mechanisms, which have not yet been used in clinical settings (e.g., levetiracetam or Neu 120) (Table 1). A major breakthrough in treating Parkinson's disease cannot be expected with molecules from the first two cases, whereas significant clinical benefits can be predicted with the drugs in the last group. However, without these large-scale, well-designed, multicenter trials, the promising preclinical results cannot be directly adopted in patient care. Hopefully, some of these trials will end soon with positive results, and certain drugs will become available with which to treat PD patients, although still many aspects (e.g., the most problematic one, the question of neuroprotection) still need to be addressed.

References

1. Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, Marshall FJ, Ravina BM, Schifitto G, Siderowf A, Tanner CM (2007) Projected number of people with Parkinson's disease in the most populous nations, 2005 through 2030. Neurology 30:384–386
2. Poewe W (2009) Treatments for Parkinson's disease-past achievements and current clinical needs. Neurology 72(7 Suppl):S65–S73
3. Kandinov B, Giladi N, Korczyn AD (2009) Smoking and tea consumption delay onset of Parkinson's disease. Parkinsonism Relat Disord 15:41–46
4. Picciotto MR, Zoli M (2008) Neuroprotection via nAChRs: the role of nAChRs in neurodegenerative disorders such as Alzheimer's and Parkinson's disease. Front Biosci 13:492–504
5. Hong DP, Fink AL, Uversky VN (2009) Smoking and Parkinson's disease: does nicotine affect alpha-synuclein fibrillation? Biochim Biophys Acta 1794:282–290
6. Villafane G, Cesaro P, Rialland A, Baloul S, Azimi S, Bourdet C, Le Houezec J, Macquin-Mavier I, Maison P (2007) Chronic high dose transdermal nicotine in Parkinson's disease: an open trial. Eur J Neurol 14:1313–1316
7. Vieregge A, Sieberer M, Jacobs H, Hagenah JM, Vieregge P (2001) Transdermal nicotine in PD: a randomized, double-blind, placebo-controlled study. Neurology 57:1032–1035
8. Ebersbach G, Stöck M, Müller J, Wenning G, Wissel J, Poewe W (1999) Worsening of motor performance in patients with Parkinson's disease following transdermal nicotine administration. Mov Disord 14:1011–1013
9. Bordia T, Campos C, Huang L, Quik M (2008) Continuous and intermittent nicotine treatment reduces L-3, 4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias in a rat model of Parkinson's disease. J Pharmacol Exp Ther 327:239–247
10. Quik M, O'Leary K, Tanner CM (2008) Nicotine and Parkinson's disease: implications for therapy. Mov Disord 23:1641–1652
11. Klivenyi P, Matthews RT, Wermer M, Yang L, MacGarvey U, Becker DA, Natero R, Beal MF (1998) Azulenyl nitrone spin traps protect against MPTP neurotoxicity. Exp Neurol 152:163–166
12. Ascherio A, LeWitt PA, Watts A, Kieburtz K, Rudolph A, Schwid SR, et al. on behalf of the PSG DATA TOP investigators (2006) CSF as well as serum urate are predictors of Parkinson's disease progression. Movement Disorders Society International Congress on Parkinson's Disease and Movement Disorders, Kyoto, Japan, 2006 LB-2
13. Schwarzschild MA, Schwid SR, Marek K, Watts A, Lang AE, Oakes D, Shoulson I, Ascherio A, Hyson C, Gorbold E, Rudolph A, Kieburtz K, Fahn S, Gauger L, Goetz C, Seibyl J, Forrest M, Ondrasik J, Parkinson Study Group PRECEPT Investigators (2008) Serum urate as a predictor of clinical and radiographic progression in Parkinson's disease. Arch Neurol 65:716–723
14. Klivenyi P, Ferrante RJ, Matthews RT, Bogdanov MB, Klein AM, Andreassen OA, Mueller G, Wermer M, Kaddurah-Daouk R, Beal MF (1999) Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. Nat Med 5:347–350
15. Matthews RT, Ferrante RJ, Klivenyi P, Yang L, Klein AM, Mueller G, Kaddurah-Daouk R, Beal MF (1999) Creatine and cyclocreatine attenuate MPTP neurotoxicity. Exp Neurol 157:142–149
16. Andreassen OA, Dedeoglu A, Ferrante RJ, Jenkins BG, Ferrante KL, Thomas M, Friedlich A, Browne SE, Schilling G, Borchelt DR, Hersch SM, Ross CA, Beal MF (2001) Creatine increase survival and delays motor symptoms in a transgenic animal model of Huntington's disease. Neurobiol Dis 8:479–491
17. Klivenyi P, Calingasan NY, Starkov A, Stavrovskaya IG, Kristal BS, Yang L, Wieringa B, Beal MF (2004) Neuroprotective mechanisms of creatine occur in the absence of mitochondrial creatine kinase. Neurobiol Dis 15:610–617
18. Shefner JM, Cudkowicz ME, Schoenfeld D, Conrad T, Taft J, Chilton M, Urbinelli L, Qureshi M, Zhang H, Pestronk A, Caress J, Donofrio P, Sorenson E, Bradley W, Lomen-Hoerth C, Pioro E, Rezania K, Ross M, Pascuzzi R, Heiman-Patterson T, Tandan R, Mitsumoto H, Rothstein J, Smith-Palmer T, MacDonald D, Burke D, NEALS Consortium (2004) A clinical trial of creatine in ALS. Neurology 63:1656–1661
19. Tabrizi SJ, Blamire AM, Manners DN, Rajagopalan B, Styles P, Schapira AH, Warner TT (2005) High-dose creatine therapy for Huntington disease: a 2-year clinical and MRS study. Neurology 64:1655–1656

20. NINDS NET-PD Investigators (2006) A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease: 18-month results. Neurology 66:664–671
21. Miller JW, Selhub J, Nadeau MR, Thomas CA, Feldman RG, Wolf PA (2003) Effect of L-dopa on plasma homocysteine in PD patients: relationship to B-vitamin status. Neurology 60:1125–1129
22. Sauer J, Mason JB, Choi SW (2009) Too much folate: a risk factor for cancer and cardiovascular disease? Curr Opin Clin Nutr Metab Care 12:30–36
23. Savola JM, Hill M, Engstrom M, Merivuori H, Wurster S, McGuire SG, Fox SH, Crossman AR, Brotchie JM (2003) Fipamezole (JP-1730) is a potent alpha2 adrenergic receptor antagonist that reduces levodopa-induced dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. Mov Disord 18:872–883
24. Sato Y, Kikuyama M, Oizumi K (1997) High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease. Neurology 49:1273–1278
25. Evatt ML, Delong MR, Khazai N, Rosen A, Triche S, Tangpricha V (2008) Prevalence of vitamin D insufficiency in patients with Parkinson's disease and Alzheimer disease. Arch Neurol 65:1348–1352
26. Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, Juncos JL, Nutt J, Shoulson I, Carter J, Kompoliti K, Perlmutter JS, Reich S, Stern M, Watts RL, Kurlan R, Molho E, Harrison M, Lew M (2002) Parkinson Study Group. Effects of coenzyme Q10 in early Parkinson's disease: evidence of slowing of the functional decline. Arch Neurol 59:1541–1550
27. Storch A, Jost WH, Vieregge P, Spiegel J, Greulich W, Durner J, Müller T, Kupsch A, Henningsen H, Oertel WH, Fuchs G, Kuhn W, Niklowitz P, Koch R, Herting B, Reichmann H, German Coenzyme Q(10) Study Group (2007) Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q (10) in Parkinson's disease. Arch Neurol 64:938–944
28. Lyons KE, Pahwa R (2006) Efficacy and tolerability of levetiracetam in patients with levodopa-induced dyskinesia. Clin Neuropharmacol 29:148–153
29. Zesiewicz TA, Sullivan KL, Maldonado JL, Tatum WO, Hauser RA (2005) Open-label pilot study of levetiracetam (Keppra) for the treatment of levodopa-induced dyskinesias in Parkinson's disease. Mov Disord 20:1205–1209
30. Jenner P, Mori A, Hauser R, Morelli M, Fredholm BB, Chen JF (2009) Adenosine, adenosine A(2A) antagonists, and Parkinson's disease. Parkinsonism Relat Disord 15:406–413
31. Stocchi F, Vacca L, Grassini P, De Pandis MF, Battaglia G, Cattaneo C, Fariello RG (2006) Symptom relief in Parkinson's disease by safinamide: biochemical and clinical evidence of efficacy beyond MAO-B inhibition. Neurology 67(7 Suppl 2):S24–12
32. Dutoit J, Coetzee C, Grant T, Shoulson I, Rajachandran L, Tschopp R, Sprenger K, Stankovic S (2009) Safety, tolerability, efficacy and pharmacokinetics in phase 2 study of aplindore in patients with early stage of Parkinson's disease. Movement Dis Suppl.1:S263
33. Pollak L, Dobronevsky Y, Prohorov T, Bahunker S, Rabey JM (2007) Low dose methylphenidate improves freezing in advanced Parkinson's disease during off-state. J Neural Transm Suppl 72:145–148
34. Devos D, Krystkowiak P, Clement F, Dujardin K, Cottencin O, Waucquier N, Ajebbar K, Thielemans B, Kroumova M, Duhamel A, Destée A, Bordet R, Defebvre L (2007) Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson's disease. J Neurol Neurosurg Psychiatry 78:470–475
35. Auriel E, Hausdorff JM, Herman T, Simon ES, Giladi N (2006) Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. Clin Neuropharmacol 29:15–17
36. Nutt JG, Carter JH, Carlson NE (2007) Effects of methylphenidate on response to oral levodopa: a double-blind clinical trial. Arch Neurol 64:319–323
37. Auriel E, Hausdorff JM, Giladi N (2009) Methylphenidate for the treatment of and other neurological disorders. Clin Neuropharmacol 32:75–81
38. Mendonça DA, Menezes K, Jog MS (2007) Methylphenidate improves fatigue scores in Parkinson's disease: a randomized controlled trial. Mov Disord 22:2070–2076
39. Surmeier DJ (2007) Calcium, ageing, and neuronal vulnerability in Parkinson's disease. Lancet Neurol 6:933–938
40. Schuster S, Doudnikoff E, Rylander D, Berthet A, Aubert I, Ittrich C, Bloch B, Cenci MA, Surmeier DJ, Hengerer B, Bezard E (2009) Antagonizing L-type Ca2+ channel reduces development of abnormal involuntary movement in the rat model of L-3, 4-dihydroxyphenylalanine-induced dyskinesia. Biol Psychiatry 65:518–526
41. Stocchi F, Fabbri L, Vecsei L, Krygowska-Wajs A, Monici Preti PA, Ruggieri SA (2007) Clinical efficacy of a single afternoon dose of effervescent levodopa-carbidopa preparation (CHF 1512) in fluctuating Parkinson's disease. Clin Neuropharmacol 30:18–24
42. Hodgson RA, Bertorelli R, Varty GB, Lachowicz JE, Forlani A, Fredduzzi S, Cohen-Williams ME, Higgins GA, Impagnatiello F, Nicolussi E, Parra LE, Foster C, Zhai Y, Neustadt BR, Stamford AW, Parker EM, Reggiani A, Hunter JC (2009) Characterization of the potent and highly selective A2A receptor antagonists preladenant and SCH 412348 in rodent models of movement disorders and depression. J Pharmacol Exp Ther 330:294–303
43. Németh H, Toldi J, Vécsei L (2006) Kynurenines, Parkinson's disease and other neurodegenerative disorders: preclinical and clinical studies. J Neural Transm Suppl 70:285–304
44. Robotka H, Toldi J, Vecsei L (2008) L-kynurenine: metabolism and mechanism of neuroprotection. Future Neurol 3:169–188
45. Vecsei L (2005) Kynurenines in the brain: from experiments to clinics. NOVA, New York
46. Ogawa T, Matson WR, Beal MF, Myers RH, Bird ED, Milbury P, Saso S (1992) Kynurenine pathway abnormalities in Parkinson's disease. Neurology 42:1702–1706
47. Hadj Tahar A, Grégoire L, Darré A, Bélanger N, Meltzer L, Bédard PJ (2004) Effect of a selective glutamate antagonist on L-dopa-induced dyskinesias in drug-naive parkinsonian monkeys. Neurobiol Dis 15:171–176
48. Grégoire L, Rassoulpour A, Guidetti P, Samadi P, Bédard PJ, Izzo E, Schwarcz R, Di Paolo T (2008) Prolonged kynurenine 3-hydroxylase inhibition reduces development of levodopa-induced dyskinesias in parkinsonian monkeys. Behav Brain Res 186:161–167