# Current Management of the Cognitive Dysfunction in Parkinson's Disease: How Far Have We Come?

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MINIREVIEW

# Current Management of the Cognitive Dysfunction in Parkinson's Disease: How Far Have We Come?

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**Parkinson's disease (PD) clinical features comprise both motor and nonmotor manifestations. Among the nonmotor complications, dementia is the most important. Approximately 40% of PD patients are affected by cognitive impairment. Remarkably, in addition to age, dementia is an independent predictor of mortality, whereas age at onset of PD and severity of neurological symptoms are not. In this review, I summarize the current knowledge of the pathogenesis of the PD cognitive impairment in relation to the therapies presently accessible and those that could become strategic in the near future. It is hypothesized that patients with PD show two components of cognitive dysfunction (CD): a generalized profile of subcortical dementia (PDsCD), and an overlapped pattern suggesting specific prefrontal damage with CD (PDpFCD). PDsCD is associated with structural neocortical/subcortical changes in the brain (in frontal, parietal, limbic, and temporal lobes, as well as in midbrain structures). In PDpFCD cognitive deficits comprise impairments in neuropsychological tests sensitive for frontal lobe function (discrete elements of episodic and working memory for instance), which are considered to be the consequence of dysfunction in neuronal loops connecting the prefrontal cortex and basal ganglia. Drugs reviewed for targeting PDsCD include: cholinesterase inhibitors, agents with mixed cholinergic and dopaminergic properties, anti-glutamatergic drugs, mixed antiglutamatergic/dopaminergic agents; antioxidants and enhancers of mitochondrial functions, and anti-COX-2, as well as other anti-inflammatory mediators. Preliminary studies with vehicles that may target PDpFCD include piribedil, tolcapone, amantadine, and farampator. Additional agents (citicoline and neuroimmuniphilines, among others) will be outlined. A brief overview on neuroprotection and promising new biological advances in PD (deep brain stimulation, stem cells, gene therapy) also will be summarized.** Exp Biol Med 233:941–951, 2008

**Key words:** Parkinson's disease; cognitive dysfunction; prefrontal cortex; dopamine; cholinesterase-inhibitors; ampakines

## Introduction

Parkinson's disease (PD) is a relatively common neurodegenerative disease associated with progressive loss of dopaminergic neurons of the substantia nigra (SN) and locus coeruleus. The major clinical symptoms of PD are body rigidity, hypokinesia, and postural instability linked with trembling extremities. The cause of non-familial PD remains unclear. There are several theories regarding the possible factors behind the neuronal degeneration. These include environmental toxins, genetic factors, proteasomal and mitochondrial dysfunction, as well as free radical-mediated cell death/oxidative stress. PD clinical features also comprise nonmotor manifestations among which, dementia is the most important. In approximately 40% of patients, PD is complicated by cognitive impairment (1, 2). Moreover, in addition to age, dementia is an independent predictor of mortality, whereas age at onset of PD and severity of neurological symptoms are not (3).

**Cognitive Dysfunction in PD.** Patients with PD have two components of cognitive dysfunction (CD): a generalized subcortical dementia (PDsCD), and a hypothe-

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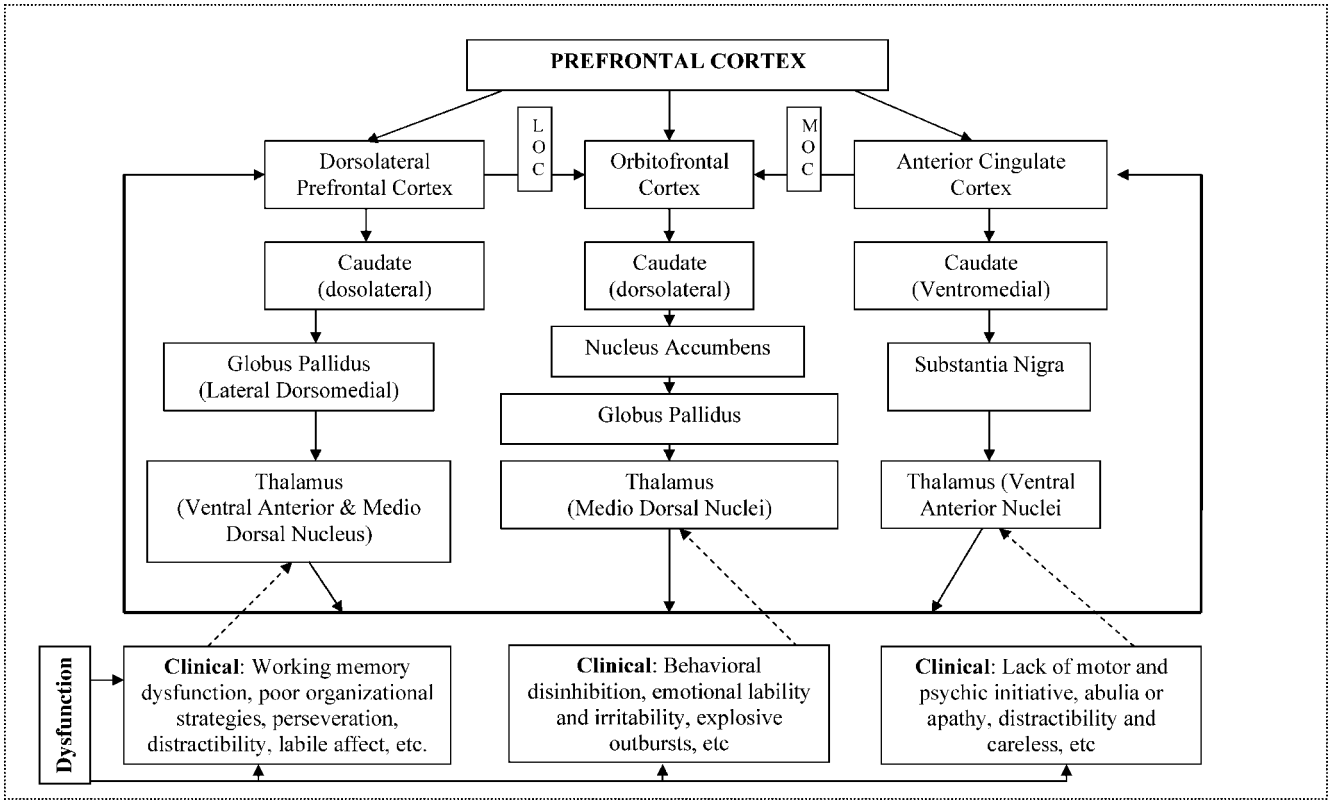


**Figure 1.** Simplified view of pathways connecting prefrontal to subcortical structures involved in different aspects of executive control. There are five brain circuits originating in the frontal lobes and linking them as functional units to subcortical structures. Two of these have primarily motor functions and are not shown here. The other three (cognitive-relevant) anatomical structures originate in prefrontal cortex, project to the striatum (caudate, putamen, ventral striatum), connect to the globus pallidus and SN, and from there connect to the thalamus. A final link back to the frontal cortex does exist, and each circuit forms a closed loop. The dorsolateral cortex receives the majority of its distant afferent inputs by means of the superior longitudinal and uncinate fasciculi, and short-range association fibers (U-fibers) mediate local prefrontal connections. Medially, the orbitofrontal cortex connects to limbic structures by means of the uncinate fasciculus and to the ventromedial cortex through U-fibers. The orbitofrontal and ventromedial cortices are reciprocally interconnected, and it is likely that both are connected with the anterior cingulate by means of fibers of the rostral cingulum. LOC, lateral orbitofrontal cortex; MOC, medial orbitofrontal cortex (83, 84).

sized, overlapped pattern, suggesting specific prefrontal dysfunction (PDpFCD).

*PDsCD.* PDsCD is considered to be multifactorial and comprises the highly selective loss of dopamine (DA) neurons in the SN, as well as losses occurring in other nervous cells such as norepinephrine neurons in locus ceruleus and dorsal motor nucleus of the vagus, the nucleus basalis of Meynert (with a pronounced depletion of cholinergic neurons), epinephrine neurons in the rostral ventral lateral medulla, and serotonin neurons in the dorsal raphe (4, 5). Thus, PDsCD is associated with structural neo-subcortical changes in the brain (in frontal, parietal, limbic, and temporal lobes, as well as in midbrain structures), whereas in PD non-demented patients, but with mild cognitive impairment (MCI), there are reduced grey matter areas in the left frontal and both temporal lobes (6).

In addition, pathological examination shows marked accumulation of cytoplasmic inclusions of proteinaceous and lipid material called Lewy bodies (LBs). LBs consist of lipids, ubiquitin, alpha-synuclein, synphilin-1, and other entangled proteins. Alpha-synuclein is a protein of unknown function and a major component of LBs. In the sporadic form of PD, cortical LBs (and Lewy neurites) are widespread and correlate with the severity of the dementia (7). It has been suggested that the accumulated pre-synaptic alpha-synuclein prefibrillar oligomers and protofibrils, not LBs themselves, are the cause of synaptic dysfunction (8), contrasting the traditional hypothesis where LBs containing alpha-synuclein, because of its association with a free radical generating metabolite of DA, initiates neurotoxicity (9). Consequently, it has been hypothesized that inhibition of early alpha-synuclein aggregation may prevent the alpha-synuclein oligomer-related toxicities (10). Amyloid plaques are also present in PD, however, since they may represent some type of comorbidity, are outside the scope of this article. The clinical characteristics of PD subcortical dementia (slowness of mental processing, forgetfulness, apathy, and, in many cases, depression) differ from those of Alzheimer dementia's type, where prominent cerebral cortical involvement produces aphasia, amnesia, agnosia, and apraxia.

*PDpFCD.* Among the complex pathophysiological mechanisms of CD in PD, the non-demented patients at an early stage of PD already show impaired vigilance and

**Table 1.** Pharmacological Studies Targeting Parkinson's Disease Cognitive Dysfunctions[a]

| Agents | Drugs | Results | References |
|---|---|---|---|
| a) Agents targeting PD subcortical dysfunction/dementia | | | |
| Acetylcholinesterase inhibitors | Donepezil | A | 16, 18 |
| | Rivastigmine | A | 15 |
| | Galantamine | A | 17 |
| Mixed cholinergic-dopaminergic enhancers | Deprenyl (selegiline) | C | 19, 22 |
| Dopamine agonists | Piribedil | B | 25–27 |
| NMDA antagonists | Memantine | B | 28 |
| | Riluzole | Negative | 30, 31 |
| Dopamine-releasing agents | Amantadine | B | 33, 34 |
| Antioxidants (and enhancers of mitochondrial function) | Vitamin E | Negative | 38 |
| | N-acetylcysteine, etc. | Not used yet | |
| | Coenzyme Q10 | Negative | 39 |
| Anti-inflammatory agents | Refecoxib, Aspirin | Negative | 41, 42 |
| b) Agents directed to improve PD prefrontal dysfunction[a] | | | |
| Dopaminergic agonists | Piribedil | B | 25–27 |
| Dopamine-releasing agents | Amantadine | D | 33 |
| Other dopaminergic drugs (COMT inhibitors) | Tolcapone | D | 14 |
| Ampakines (AMPA enhancers) | Farampator | D | 49 |
| c) Agents with theoretical neuroprotective properties in PD[a] | | | |
| Mitochondrial protection | Coenzyme Q10 | B | 53 |
| Membrane modulators | Citicoline | A-1 | 69–71 |
| New antiglutamatergic factors | Neuroimmunophilins | D | 73, 74 |

[a] Data show a selective (not exhaustive) list of pharmacological assays. A: Moderate but significant effects albeit high rate of side-effects. A-1: Moderately positive effects, at least in other brain pathologies. B: Only preliminary data exist—further research is required. C: Symptomatically positive, but without confirmed cognitive enhancement properties. D: Still in a hypothesis-generating status. COMT, catechol-O-methyltransferase; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid-type of glutamatergic receptors.

significant deficiencies in verb retrieval, abnormalities that can be the consequence of DA depletion in the striatum, disrupting the function of subcortical prefrontal networks even in absence of loss of gray matter (11, 12). These phenomena are thought to arise from de-afferentation of the prefrontal cortex from the basal ganglia. In this regard, three closed frontal-subcortical circuits link discrete areas of the frontal cortex with the striatum and other basal ganglia, and thalamic nuclei (Fig. 1). These loops are involved in functionally distinct neurobehavioral features. Disruption of projections from the dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulated/mediofrontal cortex correlate with executive dysfunction, social behavioral abnormalities, and poor motivation, respectively. These features overlap with the clinical data of PDsCD, especially in middle and advanced stages of the disease, in such a way that in most occasions it is a theoretical issue to take apart one type of CD from the other. Nevertheless, there is a central role played by prefrontal cortex in the *early* CD of PD (12). In this hypothesized PDpFCD (preferentially affecting the dorsolateral prefrontal cortex), cognitive deficits can be recognized by neuropsychological tests sensitive for frontal lobe functions.

Interestingly, the enzyme catechol-O-methyl transferase (COMT) is important for DA degradation. In the prefrontal cortex its activity is strongly related to cognitive functions. A single-nucleotide polymorphism in their encoding gene leads a valine to methionine substitution in the COMT protein, resulting in at least a threefold lower enzymatic activity. COMT Val108/158Met has been associated with better frontal lobe function conferring an advantage in several cognitive tasks. The Met allele has also been associated with superior performance in recall-based episodic memory (hippocampal) tasks (13). These data seem to indicate that anti-PD drugs with central COMT-inhibition properties warrant further studies to distinguish if they may have a distinct beneficial effect in PDpFCD (see below in the section titled "Tolcapone") (14).

**Pharmacological Agents Targeting PDsCD.** In PD, the primary cause is yet unknown; consequently, we only have secondary weapons for symptomatic benefit of the patients (Table 1).

*Cholinesterase Inhibitors.* Because cholinergic neurotransmission plays a crucial role in a variety of CNS functions, including sensory perception, motor function, cognitive processing, memory, motivation, reward, mood etc., a deficit in the function of the cholinergic system results in cognitive impairment. Consequently, enhancing the synaptic levels of acetylcholine is viewed as a key step in restoring cognitive function. Cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine [which also possess an allosteric modulation of nicotinic receptors]) increase the synaptic levels of acetylcholine through the inhibition of the enzyme cholinesterase. Unfortunately, in

several Phase III randomized studies, the addition of these inhibitors to standard anti-PD treatment led only to a modest improvement in the dementia associated with PD, but also with high rates of nausea, vomiting, and tremor (15–17). (The major instruments designed to evaluate cognition were: the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale, Mini Mental State Exam (MMSE), the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency test [targeting the major part of the "Initiation and Perseveration" dysfunction], and the Ten Point Clock-Drawing test [to detect apraxia].) Despite these modest effects in clinical studies, the addition of donepezil in MCI may result in an increase in the activity of both, the left frontal lobe and temporal lobe, demonstrated by positron emission tomography imaging studies (18). In summary, encouraging but moderated results have been obtained from studies of PDsCD patients treated with rivastigmine, donepezil, and galantamine, although large-scale controlled trials are needed to identify the timing where cholinesterase inhibitors may provide their best effects. Also, considering the need for efficient cholinergic neurotransmission in PD, the potential deleterious effects of the older, symptomatic treatments of PD with anti-cholinergic drugs should be critically reconsidered.

*Agents with Mixed Cholinergic and Dopaminergic Properties.* Selegiline: This selective irreversible inhibitor of monoamine oxidase-B possesses a wide range of pharmacological activities. Besides its dopamine-potentiating effect, it renders protection against a number of dopaminergic, cholinergic, and noradrenergic neurotoxins (19). Moreover, selegiline metabolites interferes with early apoptotic signaling events induced by various kinds of insults in cell cultures of neuroectodermal origin, hence protects cells from apoptotic death (20). Interestingly, this drug also increases acetylcholine activity and thus, improved memory-associated synaptic plasticity (21). However, there are no randomized controlled trials (RCT) with this drug in PDsCD as yet. Moreover, in a multicenter trial phase II study of selegiline transdermal system for HIV-associated cognitive impairment, this drug, although well tolerated, failed to improve CD (cognitive modifications were detected by changes in NPZ-8 score, average of norm-adjusted z-scores for Timed Gait, Grooved Pegboard, Trail-making, Symbol Digit [to detect short-memory and attentional dysfunction], and the Subject Clinical Global Impressions using a semistructured interview) (22). In summary, beneficial effects observed in PD patients treated with selegiline are primarily symptomatic rather than cognitive-enhancement.

*Dopaminergic Agonists.* Pramipexole and Piribedil: If dopaminergic drugs improve PDsCD, why does L-Dopa exposure seems to affect adversely the course of the disease? Current opinion says that the pulsatile stimulation of the striatal DA receptors caused by the short-live of L-Dopa may be partially responsible.

Accordingly, long-acting dopaminergic agonists will be indirectly neuroprotective and may improve cognition. This is the case of Pramipexole (23). Of note, because of its D3 dopamine-receptor-selectivity, this drug exerts a neurotrophic effect on cultured DA neurons by modulating the production of endogenous glial cell derived neurotrophic factor and brain-derived neurotrophic factor (BDNF), which may participate in neuroprotection (24). However, regarding its long-term cognitive improvement effects, no RCT exists yet. Conversely, research about piribedil profile does exist and is shown below, in the PDpFSD section (25–27).

*Antiglutamatergic Drugs.* Memantine, a moderate-affinity, voltage-dependent, uncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptor, has shown to benefit cognition in patients with moderate to severe Alzheimer's disease; consequently, it has been evaluated in the symptomatic treatment for the general PDsCD. An isolated report (28) describing three patients, shows improvement of both dyskinesia and PDsCD. In consequence, the hypothetical enhanced effects of adding memantine to cholinesterase inhibitors have been proposed (29), although it must be stressed that there are no hard data recommending this drug in PD CD. Remarkably, riluzole, a more potent glutamate release inhibitor as compared with memantine, have failed to improve parkinsonian symptoms or nonmotor complications like cognition (30, 31). This apparent paradox may depend on the reduced neuronal calcium influx caused by memantine (while riluzole has no effect in this area) and that calcium deregulation may contribute to the pathogenesis of CD by increasing the formation of neurotoxic oligomer forms of the amyloid β-peptide (32).

*Other Mixed Antiglutamatergic and Dopaminergic Agents.* Amantadine, which possesses NMDA receptor blocking activity as well as DA releasing properties, apparently has beneficial effects on cognition. Consequently, it has been suggested that amantadine is a reasonable option for improving cognition in several types of neurological insults (Reviewed in 33). Importantly, in one case-control study (34), the duration of amantadine exposure was positively correlated with PD duration-until-dementia as well as attenuation of its severity. Moreover, improved survival with amantadine use also has been reported (35). Amantadine appears to act through many pharmacological mechanisms. It exhibits dopaminergic, noradrenergic, and serotonergic activities, increases the availability of acetylcholine in cortical neurons, blocks monoamine oxidase A and NMDA receptors and seems to raise β-endorphin and β-lipotropin levels (36). So, more than one of these complex effects may be relevant in the treatment of PDsCD and in the presumed general survival improvement. In summary, these preliminary findings suggest that a prospective, controlled, randomized trial of amantadine's effects on PDsCD is warranted.

*Antioxidants and Enhancers of Mitochondrial Functions.* The oxyradical products derived from DA metabolism may initiate selective SN degeneration. This situation may be increased from normal parameters if the

DA from synaptic vesicles are redistributed to cytosol as the result of an exogenous toxin (methamphetamines for instance). The resulting oxidized compound, DA-quinone, reacts with the DA-transporter and synuclein. Neurons in SN are characterized by neuromelanin, a proxy of oxidative stress. This pigment is composed of DA-quinone, DA-semiquinone, lipids, and proteins. Neuromelanin avidly binds iron and a variety of other metals, which seems to explain the basis for high iron levels in the SN, and has been suggested to act as a pool for transition metals that could contribute to the oxyradical formation by the Fenton reaction (37). These oxyradical products in turn activate microglia, causing release of nitric oxide, interleukin-6, and tumor necrosis factor-α, thus becoming an important determinant of disease progress. In line with these data, *in vitro* and in some PD models, native antioxidants (reduced glutathione, N-acetylcysteine, tetrahydrobiopterin, and the enzyme superoxide dismutase) have neuroprotective properties. Unfortunately, in spite of this strong experimental evidence, in the clinic there is no RCT with these substances yet, and only vitamin E has been tested, with negative results (38). Moreover, the antioxidant and "bioenergetic" agent in the mitochondrial respiratory chain, the coenzyme Q10, has no effect either in motor function or in activities of daily living, cognition, or depressive symptoms (39). (Three main tests detected the ineffectivity of this agent: the Parkinson's Disease Questionnaire, the Global Clinical Impression score, and the Montgomery-Asberg Depression Rating Scale.)

*Anti-COX-2 and Other Anti-Inflammatory Agents.* Many persuasive findings support the view that inflammation contributes to the pathogenesis of PD. Reactive oxygen species, cytokines, and prostaglandins are released by activated microglia in experimental lesions of dopaminergic neurons in the SN of PD patients. Consequently, it is reasonable to suppose that activated glial cells can propagate the neurodegenerative process. Therefore, drugs targeting specific aspects of the glia-related cascade may be valuable against and PDsCD (40). Nevertheless, in clinical studies this class of drugs has not proved their capability to improve PD progression nor PD CD. Two recent phase III large RCT studies carried out with aspirin and refecoxib respectively are good examples of negative results using this approach (41, 42). Incidentally, in these studies, cognition modifications were comprehensively searched (41) by: Boston memory test, delayed recall, and category fluency (naming as many animals as possible in one minute); likewise, CD was extensively evaluated (42) by MMSE, Clinical Dementia Rating, Blessed Dementia Rating Scale, and Auditory Verbal Learning Test.

**Pharmacological Agents Targeting Prefrontal CD in PD (PDpFCD) (Table 1).** *Piribedil.* In PD, converging evidence from behavioral pharmacology and neuroimaging suggests that CD could, at least in part, be related to impairment of the mesolimbic and mesocortical DA pathways (43). However, PD patients are also less proficient in learning the predictive value of reward cues, despite preserved mesolimbic processing of reward prediction errors. Values and probabilities of reward outcomes are coded in a medial prefrontal-mesolimbic network and a deficit in learning expected values might be a result of both mesolimbic neurotransmitter deficiencies, and medial prefrontal dysfunction. Moreover, a functional disconnection between the prefrontal cortex and the supplementary and premotor cortex in PD patients has been disclosed (44), arguing in favor of combination of both factors PDsCD and PDpFCD, in the early CD of PD. In a brief "proof-of-concept" randomized study, 19 out of 25 patients with severe MCI showed improvement (evaluated for significance with non-parametric statistics with the "Mini-Mental State Examination" scores) taking the DA agonist piribedil (25). Since in addition to its dopaminergic activity, piribedl augments the extracellular levels of ACh in the frontal cortex and dorsal hippocampus, possibly antagonizing the alpha-2A-adrenoceptors, (these receptors exert a tonic inhibitory influence upon cholinergic transmission) (26, 27), this preliminary report deserves further studies to disclose actual usefulness in targeting PDsCD and/or PDpCD.

*Amantadine.* An isolated report showed that amantadine administration can yield prefrontal, executive function enhancement, as well as increased neuronal activity in prefrontal cortex (33). Because the study not only included tests of executive function, but also functional image analysis of frontal activity (PET data demonstrating a significant increase in left pre-frontal cortex glucose metabolism), it is reliability is reasonable. However, its open-label design and the limited number of subjects lead one to consider these results as a hypothesis-generating study, and further research is required. Of note, the main tests leading to conclude that there were cognitive improvement consisted in: Trail Making Test Part B and Controlled Oral Word Association Test [to evaluate the executive functions]; to assess the attention domain were the Trail Making Test Part A, and the Digit Span test; and finally, the memory measurements were performed by the California Verbal Learning Test and the Rey Osterreith Complex. As a final point, it is worth noting that when CD is present, amantadine (and overall DA-agonist drugs) can induce important side-effects, among which hallucinations are frequent.

*Tolcapone.* Accumulated data from electrophysiological studies in experimental animals indicates that DA "focuses and stabilizes" prefrontal cortical networks by modulating NMDA and GABAergic currents. Neuroimaging studies in pharmacological manipulations with normal humans using indirect agonists such as amphetamine, or with levodopa treatment in patients with PD, have demonstrated that increasing DA activity enhances prefrontal physiologic "efficiency." In contrast to psychostimulant drugs (e.g., amphetamine), which target all biogenic amines throughout the brain, animal studies showed that the COMT

activity of the brain appears to specifically affect extracellular DA levels, primarily in cortical regions where DA transporters are functionally negligible (45). Consequently, a specific pharmacological approach to regulate prefrontal cortical DA signaling may be achieved by increasing extracellular DA through inhibition of COMT.

Whereas many COMT inhibitors reduce the peripheral enzyme with greater potency than the enzyme present in the central nervous system, tolcapone does penetrate the blood–brain barrier and inhibits the COMT activity of the brain. A recent "proof-of-concept" study shows that this drug enhances memory and executive cognition and the physiologic efficiency of prefrontal cortical information processing in normal volunteers (14). Researchers used tests linked with prefrontal cortical processes, (notably verbal fluency, trail making, and letter number span). This randomized, double-blind, placebo-controlled trial is limited by its small sample (47 individuals). Moreover, improvements on measures of executive function and verbal episodic memory were restricted to individuals with a Val/Val genotype versus diminished cognitive performance in individuals with the Met/Met genotype. Thus, overall, the potential of pharmacologic inhibition of COMT in the long-term treatment of the CD in PD remains to be determined. Nevertheless, tolcapone being an antiparkinsonian agent, the expected next step is to assay it in PDpFCD. It is worth noting that side effects of tolcapone can go beyond diarrhea and hypotension, having the potential to cause hepatotoxicity. However, this complication has been disputed and some authors considered it infrequent (46).

*CX516 and Farampator.* The alpha-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid (AMPA)-type glutamatergic receptors have been linked to neuronal survival signaling. Although using a glutamate agonist for neuroprotection is counterintuitive, the broad cytoskeletal and synaptic damages caused by a neurotoxin (trimethyltin) can be reduced when AMPA modulation was initiated during the post-insult period. Furthermore, the extent of protection was comparable to that produced by some NMDA receptor antagonists (47). Allosteric potentiators of AMPA receptor function, a class of compounds termed ampakines, are being studied as potential treatments for enhancing cognition in schizophrenia and have also shown to be therapeutically beneficial for treating cognitive deficits in a variety of disorders (reviewed in 48). Multiple molecular pathways are involved in the activity of AMPA agonists, among which an excitatory response in prefrontal cortical neurons and a reciprocal interaction with the BDNF may be relevant for the improvement of PD CD. A recent controlled trial in healthy, elderly volunteers (16 subjects) with the ampakine farampator demonstrated that it has a significant positive effect on short-term memory functioning (using "symbol digit recall test" to measure incidental learning, "N-back task" to evaluate working memory, "verbal memory test" to asses episodic memory, and the "Visual Picture memory task" as a measure of both immediate and delayed recall); nevertheless, this drug appeared to impair episodic memory, and thus, it remains unclear if modulation of AMPA receptors with this agent has therapeutic value in the treatment of PD CD even though this is a highly active area of current research (49).

## Future Directions

**The Search for Neuroprotection in PD.** Since this disease is characterized by widespread neuronal damage, many novel mediums are intended to stop or lessen these neuronal losses and are freely classified as neuroprotectants. Neuroprotective therapies have been defined as interventions that produce enduring benefits by influencing underlying pathogenesis and thereby preventing or delaying the onset of the disease or its progression. However, disentangling the symptomatic effects of an intervention from the so-called "neuroprotective" effects as the basis for any observed benefit has proved to be a major challenge in developing a "disease-modifying" intervention. *Given that a sufficiently robust neuroprotective treatment would be equivalent to a cure, actually no biological or pharmacological method has confirmed yet an unambiguous neuroprotective action in PD.*

**Three Selected Examples of Clinical Trials Expected to Detect Neuroprotection in PD.** *1. The DATATOP Trial.* Selegiline was tested as a potential neuroprotective agent in PD based on its capacity to inhibit DA metabolism, an action that might prevent damage caused by oxidative metabolites besides providing symptomatic benefits (although neuroprotection is now attributed to selegiline's metabolite desmethylselegiline, which inhibits pro-apoptotic proteins and promotes anti-apoptotic proteins). The DATATOP study failed to demonstrate convincing evidence of a neuroprotective effect of selegiline (because of the incapacity of disentangling the symptomatic effects from true neuroprotection) (50). In a somewhat analogous study (the SIN-DEP-PAR trial) results obtained are consistent with a neuroprotective effect of selegiline, although with analogous caveats. In any event, propargylamines (like selegiline and the recently introduced rasagiline) deserve further research as possible neuroprotectants (51).

*2. The Coenzyme Q10 Trial.* In PD there is decreased staining and activity of mitochondrial complex in the SN. Coenzyme Q10 is the electron acceptor for mitochondrial complexes I and II and is reduced in mitochondria isolated from platelets of PD patients (52). In aged mice, CoQ10 attenuates MPTP induced loss of dopaminergic axons. In a preliminary study (53), data are consistent with possible slowing the progression of clinical decline in PD. These observations merit further research in prospective studies.

*3. Initial Treatment with a DA Agonist Versus Levodopa.* DA agonists have been shown to protect both dopaminergic and non-dopaminergic neurons from a variety

of toxins (54), as well as upregulating neurotrophic factors, inhibiting apoptotic cascades, and reversing ubiquitin/proteasome-dependent pathology (55). The REAL-PET study assessed PD progression using 18F-dopa PET in 186 patients randomized to treatment with ropinirole versus levodopa (56). The study demonstrated that ropinirole slowed the decline of putamenal DA storage capacity compared to levodopa and is consistent with the possibility that ropinirole slows progression of PD. However, confounding factors (ropinirole symptomatic benefits masking an increased rate of disease progression) yield doubts about a true neuroprotection of ropinirole. An analogous situation is seen in subjects initially treated with pramipexole compared to levodopa (the CALM-PD-CIT study [57]).

**Nonpharmacological Interventions Trying to Improve PD.** *Deep Brain Stimulation and Cognition.* Chronic bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus interna are effective neurosurgical procedures for treatment of motor symptoms in patients with advanced PD who cannot be satisfactorily treated with pharmacological treatments. Although long-term studies demonstrate that benefits of DBS persist for more than 5 years of follow-up, general disability still progresses from year to year, reflecting degeneration in nondopaminergic sites (58). Data concerning neuropsychological consequences of STN-DBS usually show no global cognitive deterioration, except for small groups of elderly patients where cognitive decompensation is possible or in patients with preoperative cognitive decline (59); consequently, good candidates for DBS should be patients free of dementia, major psychiatric disorders, structural brain lesions, and important general medical problems. Thus, although DBS can disrupt some pathogenic circuits in PD, it can not be considered as neuroprotectant.

*Cell Transplantation and Stem Cells Therapy.* Neuroregenerative therapies based on gene and stem cell therapy or a combination of both, we hope, may surpass limitations of the symptomatic treatment that is now used in PD. Transplantation of human fetal mesencephalic tissue from aborted fetuses (rich in primary dopaminergic neurons) in the putamen or caudate nucleus did not prove to be beneficial (60). In addition, a subset of patients developed graft-induced dyskinesias. Therefore, few (if any) cell transplantations have been carried out in PD patients in the last few years, since cell transplantation best results has turned out to be less effective than deep brain stimulation. However, the existence of endogenous neurogenesis is opening possibilities for a second cell-based approach in the treatment of neurodegeneration. It has been demonstrated that levodopa significantly restored the cell proliferation in the sub-ventricular zone (SVZ) of 6-OHDA-lesioned rats, again pointing to an important role of DA in increasing adult neurogenesis (60, 61). Successful endogenous stem cell-based therapy has result in efficient progenitor cell proliferation, dopaminergic differentiation, and survival of newly generated cells in PD models. Therefore, it may be feasible to generate dopaminergic neurons in the striatum by either recruitment of endogenous progenitors from the SVZ or stimulation of resident cells in the striatum with circumvented immunological reactions. However, many challenges still need to be overcome before this strategy can be brought into the clinic (60).

Another fascinating albeit speculative possibility comes from bone marrow-derived mesenchymal stromal cells. Whole adult bone marrow contains a mixture of hematopoietic cells in addition to nonhematopoietic marrow stromal cells (MSCs). The nonhematopoietic stromal cells are capable of differentiating into multiple mesodermal tissues, including bone, cartilage, fat, and muscle, and produce several neurotrophic factors and cytokines (62). Much of the recent interest surrounding the use of stromal cells in CNS injury began with the discovery that MSCs from humans give rise to cells with neuronal morphology and may also express neuronal or astrocytic markers *in vitro* (63). Importantly, some researchers suggest the transdifferentiation of MSCs into cells of neural lineage in humans is seen at low frequency *in vivo* (64). However, due to this complex transdifferentiation, other mechanisms of recovery may play a role in CNS lesion-repair including: neuroprotection, creation of a favorable environment for regeneration, expression of growth factors or cytokines, or vascular effects or remyelination (64). One is tempted to hypothesize that the inherent migration of MSCs to areas of neuronal stress-damaged and/or aging, may embrace a general neuronal/glial protecting instrument, addressing also disability related to the non-dopaminergic and neuroinflammatory pathology of PD (65). Again, many challenges still need to be overcome before this strategy can be evaluated beyond traumatic central nervous injury (an intense field of interest using MSCs) and be considered also in preclinical investigations in PD.

*Gene Therapy.* Since current therapies do not prevent disease progression, gene therapy in PD may offer the possibility for a significant advance in this unmet area. Adenovirus was the first vector used for gene transfer studies in PD models. However, this vector induces severe inflammatory responses in the area of injection. As a result, recombinant adeno-associated viral vectors (rAAVs) or lentiviruses of human or equine origin have been tested and have been demonstrated to be effective in providing neuroprotection in animal models of PD (66, 67). Since in humans the most important issue to be addressed is safety, a short list of phase 1 clinical gene therapy trials in PD are currently underway: rAAV-glutamic acid decarboxylase delivered to the subthalamic nucleus (Neurologix), rAAV-Aromatic-L-Amino acid decarboxylase carried into the striatum (Avigen), and rAAV-neurturin placed in the striatum (Ceregene). Importantly, while no reports of efficacy have has been presented yet, neither have there been reports of safety concerns (68). If these methodologies can yield safe and significant improvements for PD patients,

either in motor symptoms or in neuroprotection, remains to be seen.

**Preclinical Studies with Pharmacological Presumed Neuroprotective Agents.** Citicoline has been investigated as a therapy for stroke patients. Three mechanisms are postulated: (a) repair of the neuronal membrane *via* increased synthesis of phosphatidylcholine; (b) repair of damaged cholinergic neurons *via* potentiation of acetylcholine production; and (c) reduction of free fatty acid buildup at the site of stroke-induced nerve damage (69). Recent preclinical research has shown neuroprotective effects in the 6-hydroxydopamine-lesioned animal models (70). A Cochrane review concluded that citicoline was more effective than placebo for cognitive impairment in vascular dementia (71) and in a recent proof-of-concept trial of citicoline (44 cocaine-dependent outpatients with bipolar disease) improvement declarative memory come out (72). Accordingly, this agent warrants to be further studied in PD.

Immunophilins are ubiquitous cytosolic proteins particularly concentrated in neural tissue (neuroimmunophilins). GPI-1046 (as well as other synthetic non-immunosuppressive immunophilins derived from the immunosuppressant FK506–tacrolimus) exerts neuroprotective and neuroregenerative actions in several monoamine cellular pathways. One of its relevant actions is the suppression of synaptic glutamate transmission; thus, the prevention of excitotoxicity depends on rapid removal of glutamate by high affinity $Na^+$-dependent transporters. Since GPI-1046 was found to be significantly neuroprotective in a mouse peripheral-sympathetic nerve injury model induced by 6-hydroxydopamine, it has been speculated that these effects deserve to be explored in the treatment of PD (73). A phase II clinical trial in early PD patient has been funded by the National Institute of Neurological Disorders and Stroke and remains in development (74, 75).

The search of new therapeutic agents for treating PD is intense. Many new pharmacological agents designed to improve cognition in different diseases are in development; however, because of space limitations I refer the reader to recent reviews on the theme (76–79). As a final point, since all of the efforts of drugs development for CD are still focused on symptomatic treatment (not on biological bases) it should be stressed that understanding of the pathogenesis of the CD in PD is urgently needed in order to hasten novel drug discovery.

**Differential Diagnosis in Overlapping Diseases.** CD or dementia, rather than constituting discrete entities, are labels for a variety of neurological conditions associated with different patterns of cognitive deterioration, such as Alzheimer's disease, frontotemporal dementia, and many others. Specific neuropsychological deficits can be related to atrophy or hypoactivity of circumscribed brain regions. Since the outcome of the treatment for these diseases may be different, the correct diagnosis is essential. In this regard, a cognitive bedside assessment useful in differential diagnosis is the Addenbrooke's Cognitive Examination (82). An area in which this test has been particularly useful is that of atypical parkinsonian syndromes, such as progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, and dementia with LB. The main cognitive changes in these patients affect frontal-executive *plus visuospatial functions*. The cognitive picture of corticobasal degeneration and dementia with LB is complex and characterized, in addition to the reduction in verbal fluency, by deficits in attention/orientation (dementia with LB), language (corticobasal degeneration), and visuospatial functions (corticobasal degeneration and dementia with LB).

**Do the Results Discussed in This Paper Support Modifications in Present Therapy for PD?** At present, we have effective dopaminergic agents that can improve the parkinsonian symptoms associated with the progressive loss of the SN and locus coeruleus' neurons, and they work reasonably well over ~10 years. What is the reason that thereafter an accelerated deterioration in motor and nonmotor symptoms occurs? Therapy directed exclusively at mechanisms specific to dopaminergic cells may slow the loss of these cells but will have little effect on the development or progression of the nondopaminergic features. Consequently, we need innovative therapies directed at the underlying degenerative process (e.g., at oligomers and protofibrils aggregation, or proteasomal dysfunction, etc.) which would be expected to slow the cell damage also in these non-striatum sites. Such combination of neuroprotective strategies directed at both the primary neurodegenerative cellular mechanisms and DA-specific mechanisms might be expected to be more successful in slowing the progression of all the disease's features (80).

Nevertheless, since the primary cause of PD remains unclear, we do not have true neuroprotective agents that may work in the nondopaminergic area of the disease yet. Therefore, the question of what (if any) role do the already known drugs with limited or putative neuroprotective properties may play in the treatment of PD remains an open one. Maybe we can consider the early addition of citicoline to dopaminergic treatments in PD patients (71, 72). Amantadine or memantine may also deserve consideration in this regard (29, 34, 35). The use of other agents like N-acetylcysteine or some new agents such as sarizotan and others, unfortunately, should await further research.

## Final Remarks

1. PD is not a single entity simply resulting from a dopaminergic deficit; rather it is most likely caused by a combination of genetic and environmental factors, and cognitive performance is an aspect of brain function that is subject to a variety of influences from the social to the molecular. Physical activity, learning, and social factors exert alterations in gene expression, giving rise to changes in patterns of neural connectivity and functionality throughout life, even in aged and diseased brains. Also, dietary

regulation, cessation of smoking, treatment of depression when present, control of hypertension, folic acid plus vitamin B12 supplementation, are main tactics that should be implemented, in addition to pharmacological approaches in PD CD.

2. It has been convincingly demonstrated that normal aging decreases DA activity in frontal lobes, causing reduced "flexibility/adaptability" in daily life duties (80). Therefore, it is reasonable to consider that some of the drugs reviewed herein may improve the mild CD ongoing in some "normal" old people in whom dopaminergic activity may be reduced (81).

3. In PD, the essential determinant of clinical progression is the advancing age rather than disease duration and this circumstance seems to be the cause of its long-term dismal prognosis. Also, the risk of dementia in patients with PD is higher in those with greater severity and younger age. Consequently, it is reasonable to assume that the disease process and aging on dopaminergic and nondopaminergic structures, involve a biologic interaction. Thus, studies about the pathogenic abnormalities implicated in PD should further account not only for the relative selectivity of the disease process to the SN, but also for the widespread involvement of monoaminergic and cholinergic structures in late clinical stages of the disease. This situation is well characterized by the numerous pharmacological trials that have failed thus far to show a clinically significant benefit in PD cognition. Also, these features mean that no matter how efficient a biological or pharmacological agent can be in improving cognition, if we cannot deal with the primary cause of PD (and its intersection with abnormal aging), improvements in PD-associated dementia will be only transitory and ultimately, insufficient.


1. Papapetropoulos S, Ellul J, Polychronopoulos P, Chroni E. A registry-based, case–control investigation of Parkinson's disease with and without cognitive impairment. Eur J Neurol 11:347–351, 2004.
2. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 130:1787–1798, 2007.
3. Hughes TA, Ross HF, Mindham RHS, Spokes EGS. Mortality in Parkinson's disease and its association with dementia and depression. Acta Neurol Scand 110:118–123, 2004.
4. Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M, Solin O. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. Arch Neurol 57:470–475, 2000.
5. Warren NM, Piggott MA, Perry EK, Burn DJ. Cholinergic systems in progressive supranuclear palsy. Brain 128:239–249, 2005.
6. Beyer MK, Janvin CC, Larsen JP, Aarsland D. A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. J Neurol Neurosurg Psychiatry 78:254–259, 2007.
7. Guo L, Itaya M, Takanashi M, Mizuno Y, Mori H. Relationship between Parkinson disease with dementia and dementia with Lewy bodies. Parkinsonism Relat Disord 11:305–309, 2005.
8. Kramer ML, Schulz-Schaeffer WJ. Presynaptic alpha-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies. J Neurosci 27:1405–1410, 2007.
9. Burke WJ, Li SW, Williams EA, Nonneman R, Zahm DS. 3,4-Dihydroxyphenylacetaldehyde is the toxic dopamine metabolite in vivo: implications for Parkinson's disease pathogenesis. Brain Res 989: 205–213, 2003.
10. Danzer KM, Haasen D, Karow AR, Moussaud S, Habeck M, Giese A, Kretzschmar H, Hengerer B, and Kostka M. Different species of alpha-synuclein oligomers induce calcium influx and seeding. J Neurosci 27: 9220–9232, 2007.
11. Bruck A, Kurki T, Kaasinen V, Vahlberg T, Rinne JO. Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment. J Neurol, Neurosurg Psychiatry 75:1467–1469, 2004.
12. Cotelli M, Borroni B, Manenti R, Zanetti M, Arevalo A, Cappa SF, Padovani A. Action and object naming in Parkinson's disease without dementia. Eur J Neurol 14:632–637, 2007.
13. Schott BH, Seidenbecher CI, Fenker DB, Lauer CJ, Bunzeck N, Bernstein HG, Tischmeyer W, Gundelfinger ED, Heinze HJ, Duzel E. The dopaminergic midbrain participates in human episodic memory formation: evidence from genetic imaging. J Neurosci 26:1407–1417, 2006.
14. Apud JA, Mattay V, Chen J, Kolachana BS, Callicott JH, Rasetti R, Alce G, Iudicello JE, Akbar N, Egan MF, Goldberg TE, Weinberger DR. Tolcapone improves cognition and cortical information processing in normal human subjects. Neuropsychopharmacology 32:1011–1020, 2007.
15. Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, Durif F, Kulisevsky J, van Laar T, Lees A, Poewe W, Robillard A, Rosa MM, Wolters E, Quarg P, Tekin S, Lane R. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 351:2509–2518, 2004.
16. Leroi I, Brandt J, Reich SG, Lyketsos CG, Grill S, Thompson R, Marsh L. Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. Int J Geriatr Psychiatry 19:1–8, 2004.
17. Kaufer DI. Pharmacologic treatment expectations in the management of dementia with Lewy bodies. Dement Geriatr Cogn Disord 17(Suppl 1): 32–39, 2004.
18. Chen X, Magnotta VA, Duff K, Boles Ponto LL, Schultz SK. Donepezil effects on cerebral blood flow in older adults with mild cognitive deficits. J Neuropsychiatry Clin Neurosci 18:178–185, 2006.
19. Magyar K, Palfi M, Tabi T, Kalasz H, Szende B, Szoko E. Pharmacological aspects of (-)-deprenyl. Curr Med Chem 11:2017–2031, 2004.
20. Tatton WG. Selegiline can mediate neuronal rescue rather than neuronal protection. Mov Disord 8:S20–S30, 1993.
21. Murphy KJ, Foley AG, O'Connell AW, Regan CM. Chronic exposure of rats to cognition enhancing drugs produces a neuroplastic response identical to that obtained by complex environment rearing. Neuropsychopharmacology 31:90–100, 2006.
22. Schifitto G, Zhang J, Evans SR, Sacktor N, Simpson D, Millar LL, Hung VL, Miller EN, Smith E, Ellis RJ, Valcour V, Singer E, Marra CM, Kolson D, Weihe J, Remmel R, Katzenstein D, Clifford DB; ACTG A5090 Team. A multicenter trial of selegiline transdermal system for HIV-associated cognitive impairment. Neurology 69:1314–1321, 2007.
23. Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA 287:1653–1661, 2002.
24. Du F, Li R, Huang Y, Li X, Le W. Dopamine D3 receptor-preferring agonists induce neurotrophic effects on mesencephalic dopamine neurons. Eur J Neurosci 22:2422–2430, 2005.
25. Nagaraja D, Jayashree S. Randomized study of the dopamine receptor

agonist piribedil in the treatment of mild cognitive impairment. Am J Psychiatry 158:1517–1519, 2001.
26. Turle-Lorenzo N, Maurin B, Puma C, Chezaubernard C, Morain P, Baunez C, Nieoullon A, Amalric M. The dopamine agonist piribedil with L-DOPA improves attentional dysfunction: relevance for Parkinson's disease. J Pharmacol Exp Ther 319:914–923, 2006.
27. Gobert A, Di Cara B, Cistarelli L, Millan MJ. Piribedil enhances frontocortical and hippocampal release of acetylcholine in freely moving rats by blockade of alpha 2A-adrenoceptors: a dialysis comparison to talipexole and quinelorane in the absence of acetylcholinesterase inhibitors. J Pharmacol Exp Ther 305:338–346, 2003.
28. Lokk J. [Memantine can relieve certain symptoms in Parkinson disease. Improvement achieved in two out of three described cases with dyskinesia and cognitive failure]. Lakartidningen 101:2003–2006, 2004.
29. Zhao X, Marszalec W, Toth PT, Huang J, Yeh JZ, Narahashi T. In vitro galantamine-memantine co-application: mechanism of beneficial action. Neuropharmacology 51:1181–1191, 2006.
30. Braz CA, Borges V, Ferraz HB. Effect of riluzole on dyskinesia and duration of the on state in Parkinson disease patients: a double-blind, placebo-controlled pilot study. Clin Neuropharmacol 27:25–29, 2004.
31. Bara-Jimenez W, Dimitrova TD, Sherzai A, Aksu M, Chase TN. Glutamate release inhibition ineffective in levodopa-induced motor complications. Mov Disord 21:1380–1383, 2006.
32. Isaacs AM, Senn DB, Yuan M, Shine JP, Yankner BA. Acceleration of amyloid beta-peptide aggregation by physiological concentrations of calcium. J Biol Chem 281:27916–27923, 2006.
33. Kraus MF, Smith GS, Butters M, Donnell AJ, Dixon E, Yilong C, Marion D. Effects of the dopaminergic agent and NMDA receptor antagonist amantadine on cognitive function, cerebral glucose metabolism and D2 receptor availability in chronic traumatic brain injury: a study using positron emission tomography (PET). Brain Inj 19:471–479, 2005.
34. Inzelberg R, Bonuccelli U, Schechtman E, Miniowich A, Strugatsky R, Ceravolo R, Logi C, Rossi C, Klein C, Rabey JM. Association between amantadine and the onset of dementia in Parkinson's disease. Mov Disord 21:1375–1379, 2006.
35. Uitti RJ, Rajput AH, Ahlskog JE, Offord KP, Schroeder DR, Ho MM, Prasad M, Rajput A, Basran P. Amantadine treatment is an independent predictor of improved survival in Parkinson's disease. Neurology 46: 1551–1556, 1996.
36. Huber TJ, Dietrich DE, Emrich HM. Possible use of amantadine in depression. Pharmacopsychiatry 32:47–55, 1999.
37. Sulzer D, Bogulavsky J, Larsen KE, Behr G, Karatekin E, Kleinman MH, Turro N, Krantz D, Edwards RH, Greene LA, Zecca L. Neuromelanin biosynthesis is driven by excess cytosolic catecholamines not accumulated by synaptic vesicles. Proc Natl Acad Sci U S A 97:11869–11874, 2000.
38. Vatassery GT, Bauer T, Dysken M. High doses of vitamin E in the treatment of disorders of the central nervous system in the aged. Am J Clin Nutr 70:793–801, 1999.
39. Storch A, Jost WH, Vieregge P, Spiegel J, Greulich W, Durner J, Muller T, Kupsch A, Henningsen H, Oertel WH, Fuchs G, Kuhn W, Niklowitz P, Koch R, Herting B, Reichmann H; for the German Coenzyme Q10 Study Group. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q10 in Parkinson disease. Arch Neurol 64:938–944, 2007.
40. Chen H, Zhang SM, Hernan MA, Schwarzschild MA, Willett WC, Colditz GA, Speizer FE, Ascherio A. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch Neurol 60:1059–1064, 2003.
41. Kang JH, Cook N, Manson J, Buring JE, Grodstein F. Low dose aspirin and cognitive function in the women's health study cognitive cohort. BMJ 334:987–994, 2007.
42. Thal LJ, Ferris SH, Kirby L, Block GA, Lines CR, Yuen E, Assaid C, Nessly ML, Norman BA, Baranak CC, Reines SA; Rofecoxib Protocol 078 Study Group. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology 30:1204–1215, 2005.
43. Schott BH, Niehaus L, Wittmann BC, Schütze H, Seidenbecher CI, Heinze HJ, Düzel E. Ageing and early-stage Parkinson's disease affect separable neural mechanisms of mesolimbic reward processing. Brain 130:2412–2424, 2007.
44. Rowe J, Stephan KE, Friston K, Frackowiak R, Lees A, Passingham R. Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. Brain 125:276–289, 2002.
45. Mattay VS, Tessitore A, Callicott JH, Bertolino A, Goldberg TE, Chase TN, Hyde TM, Weinberger DR. Dopaminergic modulation of cortical function in patients with Parkinson's disease. Ann Neurol 51:156–164, 2002.
46. Lees AJ, Ratziu V, Tolosa E, Oertel WH. Safety and tolerability of adjunctive Tolcapone therapy in early Parkinson's disease patients. J Neurol Neurosurg Psychiatry 78:944–948, 2007.
47. Munirathinam S, Rogers G, Bahr BA. Positive modulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptors elicits neuroprotection after trimethyltin exposure in hippocampus. Toxicol Appl Pharmacol 185:111–118, 2002.
48. O'Neill MJ, Witkin JM. AMPA receptor potentiators: application for depression and Parkinson's disease. Curr Drug Targets 8:603–620, 2007.
49. Wezenberg E, Verkes RJ, Ruigt GS, Hulstijn W, Sabbe BG. Acute effects of the ampakine farampator on memory and information processing in healthy elderly volunteers. Neuropsychopharmacology 32:1272–1283, 2007.
50. Parkinson Study Group. Mortality in DATATOP: a multicenter trial in early Parkinson's disease. Ann Neurol 43:318–325, 1998.
51. Olanow CW. Rationale for considering that propargylamines might be neuroprotective in Parkinson's disease. Neurology 66(Suppl 4):S69–S79, 2006.
52. Shults CW, Haas RH, Passov D, Beal MF. Coenzyme Q10 levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects. Ann Neurol 42:261–264, 1997.
53. 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; Parkinson Study Group. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 59: 1541–1550, 2002.
54. Schapira AH. Neuroprotection and dopamine agonists. Neurology 58: S9–S18, 2002.
55. Iida M, Miyazaki I, Tanaka K, Kabuto H, Iwata-Ichikawa E, Ogawa N. Dopamine D2 receptor-mediated antioxidant and neuroprotective effects of ropinirole, a dopamine agonist. Brain Res 838:51–59, 1999.
56. Whone AL, Watts RL, Stoessl AJ, Davis M, Reske S, Nahmias C, Lang AE, Rascol O, Ribeiro MJ, Remy P, Poewe WH, Hauser RA, Brooks DJ; REAL-PET Study Group. Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. Ann Neurol 54:93–101, 2003.
57. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol 61:1044–1053, 2004.
58. Aybek S, Gronchi-Perrin A, Berney A, Chiuve SC, Villemure JG, Burkhard PR, Vingerhoets FJ. Long-term cognitive profile and incidence of dementia after STN-DBS in Parkinson's disease. Mov Disord 22:S974–S981, 2007.
59. Contarino MF, Daniele A, Sibilia AH, Romito LM, Bentivoglio AR, Gainotti G, Albanese A. Cognitive outcome 5 years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 78:248–252, 2007.

60. Geraerts M, Krylyshkina O, Debyser Z, Baekelandt V. Concise review: therapeutic strategies for Parkinson disease based on the modulation of adult neurogenesis. Stem Cells 25:263–270, 2007.
61. Höglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EC. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat Neurosci 7:726–735, 2004.
62. Dormady SP, Bashayan O, Dougherty R, Zhang XM, Basch RS. Immortalized multipotential mesenchymal cells and the hematopoietic microenvironment. J Hematother Stem Cell Res 10:125–140, 2001.
63. Munoz-Elias G, Woodbury D, Black IB. Marrow stromal cells, mitosis, and neuronal differentiation: stem cell and precursor functions. Stem Cells 21:437–448, 2003.
64. Parr AM, Tator CH, Keating A. Bone marrow-derived mesenchymal stromal cells for the repair of central nervous system injury. Bone Marrow Transplantation 40:609–619, 2007.
65. Mount MP, Lira A, Grimes D, Smith PD, Faucher S, Slack R, Anisman H, Hayley S, Park DS. Involvement of interferon-gamma in microglial-mediated loss of dopaminergic neurons. J Neurosci 27:3328–3337, 2007.
66. Emborg ME, Carbon M, Holden JE, During MJ, Ma Y, Tang C, Moirano J, Fitzsimons H, Roitberg BZ, Tuccar E, Roberts A, Kaplitt MG, Eidelberg D. Subthalamic glutamic acid decarboxylase gene therapy: changes in motor function and cortical metabolism. J Cereb Blood Flow Metab 27:501–509, 2007.
67. Kordower JH, Herzog CD, Dass B, Bakay RA, Stansell J 3rd, Gasmi M, Bartus RT. Delivery of neurturin by AAV2 (CERE-120)-mediated gene transfer provides structural and functional neuroprotection and neurorestoration in MPTP-treated monkeys. Ann Neurol 60:706–715, 2006.
68. Dass B, Olanow CW, Kordower JH. Gene transfer of trophic factors and stem cell grafting as treatments for Parkinson's disease. Neurology 66(Suppl 4):S89–S103, 2006.
69. D'Orlando KJ, Sandage BW Jr. Citicoline (CDP-choline): mechanisms of action and effects in ischemic brain injury. Neurol Res 17:281–284, 1995.
70. Barrachina M, Dominguez I, Ambrosio S, Secades J, Lozano R, Ferrer I. Neuroprotective effect of citicoline in 6-hydroxydopamine-lesioned rats and in 6-hydroxydopamine-treated SH-SY5Y human neuroblastoma cells. J Neurol Sci 215:105–110, 2003.
71. Fioravanti M, Yanagi M. Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly. Cochrane Database Syst Rev 2:CD000269, 2005.
72. Brown ES, Gorman AR, Hynan LS. A randomized, placebo-controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence. J Clin Psychopharmacol 27:498–502, 2007.
73. Ganel R, Ho T, Maragakis NJ, Jackson M, Steiner JP, Rothstein JD. Selective up-regulation of the glial Na+-dependent glutamate transporter GLT1 by a neuroimmunophilin ligand results in neuroprotection. Neurobiol Dis 21:556–567, 2006.
74. Poulter MO, Payne KB, Steiner JP. Neuroimmunophilins: a novel drug therapy for the reversal of neurodegenerative disease? Neuroscience 128:1–6, 2004.
75. Johnston TH, Brotchie JM. Drugs in development for Parkinson's disease: an update. Curr Opin Investig Drugs 7:25–32, 2006.
76. Schapira AH, Bezard E, Brotchie J, Calon F, Collingridge GL, Ferger B, Hengerer B, Hirsch E, Jenner P, Le Novere N, Obeso JA, Schwarzschild MA, Spampinato U, Davidai G. Novel pharmacological targets for the treatment of Parkinson's disease. Nat Rev Drug Discov 5:845–854, 2006.
77. Gray JA, Roth BL. Molecular targets for treating cognitive dysfunction in schizophrenia. Schizophr Bull 33:1100–1119, 2007.
78. Wess J, Eglen RM, Gautam D. Muscarinic acetylcholine receptors: mutant mice provide new insights for drug development. Nat Rev Drug Discov 6:721–733, 2007.
79. Pogacić V, Herling P. List of drugs in development for neurodegenerative diseases. Update June 2007. Neurodegener Dis 4:443–486, 2007.
80. Lang AE. The progression of Parkinson disease: a hypothesis. Neurology 68:948–952, 2007.
81. Vale S. How migraines impact cognitive function: findings from the Baltimore ECA. Neurology 69:810, 2007.
82. Bak TH, Mioshi E. A cognitive bedside assessment beyond the MMSE: the Addenbrooke's Cognitive Examination. Pract Neurol 7:245–249, 2007.
83. Fellows LK. Advances in understanding ventromedial prefrontal function: the accountant joins the executive. Neurology 68:991–995, 2007.
84. Nadeau SE, Heilman KM. Frontal mysteries revealed. Neurology 68: 1450–1453, 2007.