# New Pharmacological Options for Treating Advanced Parkinson's Disease

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## ABSTRACT

**Background:** Parkinson's disease (PD) affects about 1% of the over 60 population and is characterized by a combination of motor symptoms (rest tremor, bradykinesia, rigidity, postural instability, stooped posture and freezing of gait [FoG]) and non-motor symptoms (including psychiatric and cognitive disorders). Given that the loss of dopamine in the striatum is the main pathochemical hallmark of PD, pharmacological treatment of the disease has focused on restoring dopaminergic neurotransmission and thus improving motor symptoms. However, the currently licensed medications have several major limitations. Firstly, dopaminergic medications modulate all the key steps in dopamine transmission other than the most powerful determinant of extracellular dopamine levels: the activity of the presynaptic dopamine transporter. Secondly, other monoaminergic neurotransmission systems (ie noradrenergic, cholinergic and glutamatergic systems are altered in PD and may be involved in a variety of motor and non-motor symptoms. Thirdly, today's randomized clinical trials are primarily designed to assess the efficacy and safety of treatments for motor fluctuations and dyskinesia. Fourthly, there is a need for disease- modifying treatments (DMTs) that slow disease progression and reduce the occurrence of the very disabling disorders seen in late-stage PD.

**Objective:** To systematically review a number of putative pharmacological options for treating the main impairments in late-stage PD (ie gait disorders, cognitive disorders and behavioural disorders such as apathy).

**Methods:** We searched the PubMed database up until July 2013 with logical combinations of the following search terms: "Parkinson's disease", "gait", "cognition", "apathy", "advanced stage", "modulation", "noradrenergic", "cholinergic", "glutamatergic" and "neurotransmission".

**Results:** In patients undergoing subthalamic nucleus stimulation, the potentiation of noradrenergic and dopaminergic transmission by methylphenidate improves gait and FoG and may relieve apathy. However, the drug failed to improve cognition in this population. Potentiation of the cholinergic system by acetylcholinesterase inhibitors (which are licensed for use in dementia) may reduce pre-dementia apathy and falls. Modulation of the glutamatergic system by an N-methyl-D-aspartate receptor antagonist did not improve gait and dementia but may have reduced axial rigidity. A number of putative DMTs have been reported.

**Discussion:** Novel therapeutic strategies should seek to reduce the appearance of the very disabling disorders observed in late-stage PD. Dopamine and/or noradrenaline transporter inhibitors, anticholinesterase inhibitors, Peroxisome-proliferator-activated-receptor-agonists and iron chelators should at least be investigated as putative DMTs by applying a delayed-start clinical trial paradigm to a large population

**Conclusions:** There is a need for more randomized clinical trials of treatments for late-stage PD. (*Clin Ther*. 2013;35:1640–1652) 

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**Key words:** gait, dementia, cognition, apathy, non-dopaminergic treatment, disease-modifying treatment.

## INTRODUCTION

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder worldwide and affects about 1% of the over 60s.[1] The disease is characterized by a combination of rest tremor, bradykinesia, rigidity and gait disorders. However, the clinical spectrum also encompasses non-motor symptoms, including behavioural disorders (such as apathy) and cognitive disorders.[2] The core neuropathological features of PD are the loss of dopaminergic neurons in the substantia nigra and the deposition of iron and cytoplasmic protein aggregates (Lewy bodies) inside neurons. Given that the loss of dopamine in the striatum is the main pathochemical hallmark of PD, pharmacological treatment of the disease has been focused on restoring dopaminergic neurotransmission.[3] The dopamine precursor levodopa remains the "gold standard" treatment for PD; it improves the patient's motor functions, activities of daily living and quality of life. However, levodopa also has several pharmacokinetic drawbacks (notably its short half-life). Hence, the chronic administration of levodopa required for advanced PD is frequently associated with the development of levodopa-related motor fluctuations and dyskinesia. The prevalence of these motor complications ranges from 40% to 50% after 4 to 6 years of treatment.[4,5] Inhibitors of the dopamine-metabolizing enzymes catechol-O-methyltransferase and monoamine oxidase-B (MAO-B) have been developed with a view to prolonging the half-life of levodopa and thus limiting motor fluctuations. Dopamine agonists directly stimulate postsynaptic dopamine receptors in the striatum, in order to decrease the need for levodopa and limit the appearance of motor complications.[4,6,7] However, the dopamine agonists' safety profile provides cause for concern, since these medications may variously induce impulse control disorders (ICDs), confusion, hallucinations, psychosis, excessive daytime sleepiness and sleep attacks.[4,8] Deep brain stimulation of the subthalamic nucleus (STN) (or, to a lesser extent, the internal globus pallidus) is a proven, very effective means of controlling motor complications.[9] However, the contraindications for this treatment limit its application to just a small proportion of PD patients. Continuous, subcutaneous apomorphine infusion is an effective treatment option for motor fluctuations but again is also only used with a small proportion of PD patients - probably because apomorphine is a dopaminergic agonist and the infusion pump is an external device. Earlier introduction of this treatment should nevertheless be considered.[10] Duodenal levodopa infusion* appears to be a very effective therapy for motor complications. However, poor user-friendliness (a heavy, external pump and the need for gastrostomy) restricts Duodopa® to use as a last-line therapy.[11] Lastly, a number of licensed and unlicensed drugs have also been proposed (often with a low level of scientific evidence) for the treatment of non-motor symptoms (for a review, see [12]).

The beneficial, long-term effects of currently licensed medications are often countered by the appearance of gait, cognitive and behavioural disorders as the disease progresses. This may prompt institutionalization and constitutes a public health issue.[13,14] The associated *gait disorders* are mainly characterized by impaired stride length regulation and thus a slower walking speed (ie gait hypokinesia).[15] Furthermore, freezing of gait (FoG, ie a brief, involuntary, episodic absence of (or a marked reduction in) forward progression of the foot) can also be prominent.[16] Although the disease mechanism underlying for FoG is not fully understood, several different factors are clearly involved. Gait disorders associated with FoG appear to be mainly related to disease severity and a hypodopaminergic state.[17] Optimization of levodopa treatment is the main therapeutic option under these circumstances.[16,17] However, the option of increasing the levodopa dose may be significantly restricted by (i) the worsening of levodopa-related motor complications, (ii) induction of confusion or sleepiness and (iii) progressive loss of efficacy as the disease worsens. Patients with PD have an almost six-fold greater risk of developing *dementia* than age-matched, healthy controls do.[18] In cross-sectional studies, 30% to 40% of PD patients meet the criteria for dementia.[14] Moreover, a number of longitudinal studies have revealed that the cumulative incidence of dementia in patients with PD increases with age and disease duration and can even reach 80% to 90%.[19–21] The cognitive profile in PD dementia (PDD) differs from that in Alzheimer's disease (AD) and is dominated by severe impairments in attention and in executive and visuospatial functions; in contrast, memory encoding,

*Duodopa® (Solvay Pharmaceuticals, Pymble, Australia).