# Future Treatment of Parkinson's Disease

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**ABSTRACT:** New methods of drug delivery and slowing down the progression of Parkinson's disease (PD) are the major goals of research. More steady drug levels in the blood are possible by means of controlled-release preparations of levodopa and long-acting dopamine agonists, as well as transcutaneous duodenal tubes and pumps for controlled subcutaneous infusion. Patches containing dopamine agonists absorbed through the skin may be developed. The role of D1 agonists as compared with D2 agonists remains to be elucidated. Agonists on autoreceptors of dopaminergic neurons may potentially reduce excessive stimulation of the intact neurons and this may slow down the rate of neuronal death in PD. Monoamine oxidase-B inhibitors may have a potentially protective action on neurons. Investigations are being carried out to evaluate this claim. Catechol-o-methyl-transferase inhibitors may be helpful in theory. There is also recent interest in inhibitors of excitatory amino acids, which may contribute to neuronal loss in PD.

**RÉSUMÉ: Avenir du traitement de la maladie de Parkinson.** Les buts les plus importants de la recherche sont les nouvelles méthodes d'administration de la médication et le ralentissement de la progression de la maladie de Parkinson (MP). Des taux sanguins de médication plus stables sont possibles par le biais de préparations de lévodopa à libération contrôlée et d'agonistes de la dopamine à longue action, ainsi que par cathéter duodénal percutané et pompe pour infusion sous-cutanée contrôlée. Un système transdermique, ou "patch", contenant des agonistes de la dopamine constitue une autre possibilité. Le rôle des agonistes D1 comparé à celui des agonistes D2 reste à élucider. Les agonistes agissant sur les autorécepteurs des neurones dopaminergiques peuvent potentiellement réduire la stimulation excessive des neurones sains et ceci pourrait ralentir le taux de mort neuronale dans la MP. Les inhibiteurs de la monoamine oxydase-B peuvent avoir un effet potentiellement protecteur sur les neurones. Des recherches sont en cours pour évaluer cette assertion. Les inhibiteurs de la catéchol-o-méthyl-transférase peuvent théoriquement être utiles. Il y a également un intéret récent pour les inhibiteurs des acides aminés excitateurs qui peuvent contribuer à la perte neuronale dans la MP.

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Levodopa has been the mainstay of therapy for PD over the past 2 decades. It is well known that dyskinesias and unpredictable fluctuations in symptoms and response to levodopa occur usually after 5 to 7 years of therapy.[1] Bromocriptine was introduced in the 70's[2] and it has become the yardstick for developing other newer dopamine agonists which differ in potency, selectivity and routes of administration. The observation that 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP) induces parkinsonism[3] supports the theory that PD may be initiated by a toxic injury to the basal ganglia before its onset, and symptoms only manifest years after the initial insult.[4] A wave of research has arisen to study therapeutic approaches to slow down the rate of progression of PD. Implantation of adrenal medulla autografts[5,6] dominated the surgical treatment of PD for some time, only to yield to more carefully investigated fetal cell transplantation in recent years. This manuscript will not discuss surgical approaches to treatment.

## Levodopa Therapy

Twenty years have passed since the introduction of levodopa[7,8] and it remains the most effective drug for symptomatic relief of parkinsonian symptoms. Concomitant administration of decarboxylase inhibitors[9,10] reduces the dose of levodopa required to achieve a therapeutic effect. Whether levodopa preparations should be administered to patients as soon as a diagnosis of PD is made[11] or delayed for as long as possible[12] is still debatable. There are also indications that combining low doses of levodopa and dopamine agonist such as bromocriptine will enable each drug to be taken at lower doses than would have been required when given alone; this may result in fewer long term treatment problems.[13,14] With the recent report that deprenyl can delay the necessity to initiate symptomatic therapy in newly diagnosed patients[15,16] there arises another strategy in management which is to give this drug to patients before they need any symptomatic treatment.

The effect of dietary protein on the efficacy of levodopa has been reported previously.[17] More recently, a double-blind study[18] confirmed that heavy protein meals reduce the therapeutic response of levodopa. In some selected patients who have developed fluctuations in parkinsonian symptoms, manipulating the daily protein intake so that they take less protein during the day and have the balance of their daily requirement at dinner may help to improve their activity in the day time.

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Delivery of a more steady blood level of levodopa is theoretically superior to a pulsatile level. This is achieved by administering controlled-release preparations of levodopa. Better control with more functional ("on") hours and improved performance with these preparations have been reported.[19,20]

### Dopamine Agonists

Bromocriptine,[2] Lisuride,[21] and Pergolide[22] are dopamine agonists that have been reported useful in PD. Side effects are similar in this group of drugs, and include nausea, vomiting, postural hypotension, hallucinations, and dyskinesia. Newer dopamine agonists are currently under investigation and research includes the following topics:

*Smooth Drug Levels in Blood Via Parenteral Administration*

Externally-carried infusion pumps connected to needles inserted subcutaneously on the abdominal wall have been employed to deliver a steady level of Lisuride in some patients, and have been reported to benefit patients with otherwise intractable fluctuations.[23] However, subcutaneous nodules develop easily in the abdominal wall and limit the practicality of this method of treatment. Apomorphine infusion has also been administered to patients subcutaneously or intravenously.[24] Its effects are rapid and predictable, but its potent emetic action is frequently an intolerable side effect. More recently, British researchers have reported its use to predict the response of patients to dopaminergic agents.[25] Another approach is the development of dopamine agonists which may be absorbed through the skin. It is hoped that drugs similar to (+)-4-propyl-9-hydroxynaphthoxazine (PHNO)[26,27] will be developed in future.

*Long Acting Agonists*

Dopamine agonists with long half lives may be advantageous in that they would maintain relatively constant plasma levels. Cabergoline[28] is a drug with a half life of 72 hours and it has the added advantage of once-daily administration. This drug is currently under investigation.

*Selective D1 vs D2 Stimulation*

The currently available dopamine agonists for the treatment of PD act predominantly on D2 receptors. However, it has been suggested that a background D1 stimulation may enhance the effects of D2 stimulation.[29] SKF 28292, a D1 agonist, did not benefit MPTP monkeys and PD patients.[30,31] Another selective D1 agonist, CY 208-243 has been reported to improve the symptoms of parkinsonian patients with low potency.[32] The role of D1 versus D2 stimulation remains to be elucidated.

*Autoreceptor Stimulation*

In the intact dopamine system, autoreceptors on cell bodies of dopaminergic neurons, when stimulated, reduce firing rates, while those on presynaptic membranes inhibit synthesis and the release of dopamine. Selective autoreceptor stimulation is now possible with agents such as BHT-920 and SND-919. The unique property of this class of drugs is that in the intact dopaminergic neuron, reduction of dopamine release results. However, in chronic denervation, post-synaptic dopamine receptors are stimulated and therapeutic effects may be observed. Theoretically, this would stimulate the denervated post-synaptic receptors while inhibiting neurons and thus protecting them from accelerated damage through excessive excitation.

### Monoamine Oxidase-B Inhibitors

The animal model of PD is best represented by MPTP-monkeys. MPTP is converted into MPP+, a free radical which has been demonstrated to be toxic to the dopaminergic neurons in the basal ganglia. Monoamine oxidase-B (MAO-B) is involved in the conversion, and by blocking this enzyme with deprenyl (selegiline), MPTP toxicity may be prevented. Reports are also available that deprenyl delays the necessity to initiate active symptomatic therapy in newly diagnosed parkinsonian patients.[15,16] Current controversy exists[33] regarding the interpretation of this study and the claim that this drug slows down the rate of progression of PD. The critical point pivots on whether deprenyl has any symptomatic therapeutic effects with very low potency, since this possibility could easily explain the delay in initiating active therapy in newly diagnosed patients taking deprenyl. Further studies concentrating on longer washout periods in patients taking this medication are being carried out to clarify this issue.

### Catechol-O-Methyl Transferase Inhibitors

Catechol-O-methyl transferase (COMT) is an enzyme along the pathway of the breakdown of dopamine, resulting in formation of 3-O-methyldopa (OMD). High circulating levels of OMD are related to reduced efficacy of levodopa.[34] Nitecapone (OR-462), a peripheral COMT inhibitor that does not cross the blood-brain barrier, has been reported to reduce peripheral OMD formation[35] thus improving access of levodopa. Its use to enhance the efficacy of levodopa is being explored.

### Antioxidants

Free radicals have been suggested to play a significant role in tissue injury and cell death.[36] Scavenging free radicals with antioxidants is another strategy to reduce the rate of neuronal death. High doses of vitamin E are still being studied by the Parkinson Study Group. There is also current interest in other compounds, such as the 21-aminosteroids (lazeroids), which inhibit lipid peroxidation reactions, which have been reported to exert a favorable influence on tissue trauma.[37]

### Excitatory Amino Acid Inhibitors

Excessive excitation can lead to neuronal death, and N-methyl-D-aspartate (NMDA) antagonists are reported to reduce neuronal damage.[38] There are abundant excitatory glutaminergic inputs from the cortex, thalamus, and brainstem to the basal ganglia. It is therefore theoretically possible that NMDA inhibition may slow down the rate of neuronal death in PD. Lamotrigine inhibits glutamate release[39] and may be useful in protecting nigral neurons in PD from further damage through excessive excitation.

## Conclusion

In the near future, research will be directed toward better symptomatic relief by new methods of drug delivery and the prevention of dyskinesias and unpredictable fluctuations by defining a standard strategy of combination drug therapy, as well as the slowing down of progression of PD by agents which potentially delay neuronal death.

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