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# Why should we use multifunctional neuroprotective and neurorestorative drugs for Parkinson's disease?

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**Abstract**

Parkinson's disease (PD) is a severe neurodegenerative disorder, with no available drugs able to prevent the neuronal cell loss characteristic in brains of patients suffering from PD. Due to the complex cascade of molecular events involved in the etiology of PD, an innovative approach towards neuroprotection or neurorescue may entail the use of multifunctional pharmaceuticals that target an array of pathological pathways, each of which is believed to contribute to events that ultimately lead to neuronal cell death. Here we discuss examples of novel multifunctional ligands that may have potential as neuroprotective and neurorestorative therapeutics in PD. The compounds discussed originate from synthetic chemistry as well as from natural sources where various moieties, identified in research to possess neuroprotective and neurorestorative properties, have been introduced into the structures of several monomodal drugs, some of which are used in the clinic.



*Keywords:* Rasagiline; Ladostigil; M30; $A_{2A}$ receptor antagonists; Dual mechanism; Adenosine; Iron chelation

## 1. Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disease with progressive loss of dopaminergic (DA-ergic) neurons in the substantia nigra pars compacta (SNpc). In patients, this depletion of neurons presents clinically with severe motor symptoms including uncontrollable resting tremor, bradykinesia, rigidity and postural imbalance [1–3]. For a review of the diagnosis and clinical features of PD, please refer to reference [3]. In idiopathic PD, these symptoms start to manifest when 70–80% of DA neurons in the SNpc are lost [4,5]. The exact etiology of PD remains to be fully elucidated, but the key theories propose either an environmental (e.g. insecticides [6–8]) or a genetic (e.g. parkin [9]) origin, or a combination of both.

The significant health expenditure associated with PD treatment [10,11], and lack of disease-modifying drugs have resulted in a real sense of urgency to discover novel therapies for the treatment or, preferably, the prevention of this disease. Currently, the only therapies approved for the treatment of PD are agents that attenuate the symptoms of the disease. The mainstay of PD treatment focuses on the replacement of lost DA with DA agonists, including L-dopa therapy, treatment with monoamine oxidase (MAO) B and catechol-O-methyltransferase inhibitors, and amantadine, thereby normalizing the patient symptomatically [10]. Tragic, but important in view of the seriousness of disease progression, is the fact that the course of the disease is not affected by the utilization of these drugs and that the loss of neurons continues unabated even as symptoms may be controlled, at least following initial treatment. Currently, no drugs with claimed neuroprotective activity have been identified or approved by the FDA for the treatment of PD [5,11]. Significantly though, recent research has suggested that some drugs used for symptomatic relief, such as rasagiline and pramipexole [12–14] in PD, and memantine [15–18] in Alzheimer's disease (AD), may also possess neuroprotective activities.

Recent literature shows a paradigm shift in the way researchers are considering the development and design of drugs to treat diseases with complex etiological pathways (i.e. diseases with multiple drug targets) [19–26]. In a pathway system with a multitude of drug targets, a drug with a single-target mechanism of action cannot always compensate or correct a complex pathway, which suggests that a complex pathway disease should be treated (1) with

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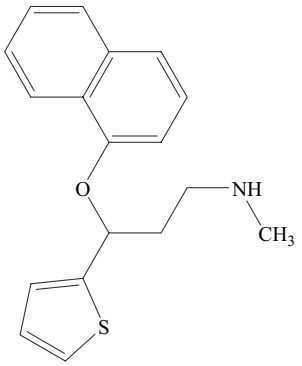
Table 1
Definitions of neuroprotective, neurorestorative and neurorescuing drugs

| Drug type | Definition |
|---|---|
| Neuroprotective | A drug that prevents or slows down neuronal death [5] |
| Neurorestorative | A drug that replaces dying or dead neuronal cells with viable cells [5] |
| Neurorescuing | A drug that rescues cells where neuronal cell death has already started [32] |

a multitude of molecules, each acting on different pathways in the disease (polypharmacy), or (2) with one molecule that possesses "promiscuous" activity acting on different pathways (multiple-mechanism drugs).

Polypharmacy is the clinical practice of combining two or more medications in a patient's medication profile, with a view to treat one specific disease, usually with each drug acting on a different drug target or by a different mechanism. For example, the combined use of salmeterol (a β2-adrenergic agonist) and fluticasone (a glucocorticoid steroid) in asthma, has led to the combination of these two medications in a single preparation. Also, the combination of simvastatin (an HMG-CoA reductase inhibitor) and ezetimibe (an inhibitor of dietary cholesterol uptake) is used to treat hyperlipidemia [19]. A new drug combination used in PD constitutes levodopa in combination with carbidopa and entacapon (a catechol-O-methyltransferase inhibitor) [27,28], an extension of the concept of the well-known levodopa/carbidopa combination alone. The major dilemma encountered in a polypharmaceutical approach, is the occurrence of a significant increase in the number of side effects, which may be significantly reduced with the use of only one compound.

The recent appearance on the market of drugs that display two mechanisms to treat a particular disease has been a clear move in the direction of the second paradigm. One example of a drug that specifically targets two neuroamine transporter systems is duloxetine. This drug is used in the treatment of depression, and inhibits both serotonin and norepinephrine uptake in the central nervous system (CNS) [29–31]. The success of drugs such as duloxetine indicates the clinical feasibility of designing multi-functional ligands to treat CNS disorders such as neurodegenerative disorders possessing complex disease pathways. We will consider examples of compounds with multi-functional neuroprotective–neurorescue properties (see Table 1 for definitions) that may have promise in the treatment of PD. Some of the compounds discussed were discovered through serendipity while others were the products of active drug design projects.




**Duloxetine (Cymbalta™)**

## 2. Propargylamines

Rasagiline is a newly approved compound for the treatment of PD [10]. Rasagiline (*N*-propargyl-1*R*-aminoindan) is an anti-PD drug with selective MAO-B inhibitory activity [33]. Its *S* isomer, TV1022 (*N*-propargyl-1*S*-aminoindan), is more than a 1,000 times less potent as an MAO inhibitor than rasagiline, but still retains neuroprotective activity, which suggests that the propargylamine moiety (even when ostensibly not involved in Michael chemistry at the FAD within the MAO catalytic site as the processing group in suicide inhibition) is responsible for the neuroprotective activity seen in both of these compounds [34–37]. The $IC_{50}$ values for inhibition of MAO by rasagiline have been reported to be: 412 nM (MAO-A rat), 4.43 nM (MAO-B rat), 710 nM (MAO-A human), and 14 nM (MAO-B human) [38]. Rasagiline has been shown to be clinically well tolerated as add-on therapy to levodopa as well as monotherapy in PD [39–41]. The maximum plasma concentration ($C_{max}$) of rasagiline is 8.5 ng/ml, which is reached in 0.5–0.7 hours. It is important to consider that rasagiline is an irreversible MAO inhibitor, of which the duration of action depends on the turnover and *de novo* synthesis of new MAO. Evidence of CNS penetration [i.e. blood–brain barrier (BBB) penetration] emanates from studies that show MAO-B inhibition $EC_{50}$ *ex vivo* values to approximate 0.042 mg/kg after a single dose injection in rats [38], as well as evidence that rasagiline, administered in the periphery, protects mice from MPTP striatal neurotoxicity [42]. For a review on the pharmacokinetics of rasagiline, see [43,44]. From these pharmacokinetic studies, it is evident that rasagiline can reach concentrations in the brain commensurate with its neuroprotective activity *in vitro* and *in vivo* [33]. To date, these neuroprotective findings are preclinical, with no patient studies to prove neuroprotective activity in the human. However, the Parkinson Study Group delayed-start study [45] with rasagiline suggested a possible disease-modifying activity for this compound.