Comparative Review of Dopamine Receptor Agonists in Parkinson’s Disease

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Summary

Limitations of long term levodopa therapy for Parkinson’s disease represent a major problem in the management of many patients. Dopamine receptor agonists provide antiparkinsonian effects and their use is most clearly defined in the con-
text of complications from levodopa therapy. As such, dopamine receptor agonists are useful adjunctive agents to levodopa. Because typical adverse effects of dopamine receptor agonists may differ from those of levodopa, combination therapy is often effective and well tolerated.

A variety of dopamine receptor agonists, both ergot and non-ergot derivatives, are useful in the treatment of Parkinson's disease. Five dopamine receptor agonists are currently available for use throughout much of the world, and many more are in developmental phases. Varying pharmacodynamic and pharmacokinetic profiles allow selection of appropriate dopamine receptor agonists for specific clinical scenarios. Recently reported comparative studies also suggest certain prescribing recommendations.

1. Dopamine Receptor Agonists

1.1 Rationale for Use

Exogenous levodopa therapy is the most efficacious treatment for nearly all patients with Parkinson's disease. However, the majority of individuals eventually develop inconsistencies in their response to the drug, with motor complications. These motor complications, including dyskinesias and motor fluctuations in the form of 'complicated end-of-dose deterioration' or 'on-off phenomenon', often result in significant patient disability. This represents a major limitation to the long term effective management of parkinsonism with levodopa alone.

Dopamine receptor agonists comprise a class of drugs that are useful in the treatment of the motor complications of levodopa therapy. They have a clear and recognised role as adjunctive therapy in patients with advanced disease and these types of levodopa-induced problems. Arguably, they may also have a role early in a patient's course when levodopa therapy is initiated; there are theoretical arguments that suggest this class of drugs may favourably affect the long term outcome of treatment in Parkinson's disease (see section 1.4).

1.2 Dopamine Receptor Subtypes

Dopamine receptors were initially divided into 2 categories based on biochemical and pharmacological data: the D₁ and D₂ classes. There was early recognition that the D₂ class primarily mediates the motor effects of central dopamine stimulation. Subsequently, other classes were identified, categorised as D₃, D₄ and D₅. Subtypes of these receptor classes are also recognised, based on cleavage patterns of their amino acid sequences.

1.2.1 Dopamine D₁ and D₂ Receptors

Dopamine has varying effects on the functional neuroanatomy of the extrapyramidal system by virtue of distinct cellular localisations of D₁ and D₂ receptors in the corticobasal ganglia-thalamocortical feedback loops. Activation of D₁ receptors has a net excitatory effect on the 'direct' pathway [striatal-medial globus pallidus/substantia nigra reticulata employing the neurotransmitters γ-aminobutyric acid (GABA), substance P and dynorphin]. In contrast, activation of D₂ receptors, which are localised to neurons projecting to the lateral globus pallidus, produces decreased firing in the 'indirect loop' (striatal-lateral globus pallidus–subthalamic nucleus–medial globus pallidus/substantia nigra reticulata employing the neurotransmitters GABA and enkephalin).

The D₁ receptor family includes not only the classical D₁ type, but also the D₃ receptor. Stimulation of either the D₁ or D₅ receptor leads to an increased formation of cyclic adenosine monophosphate (cAMP) via stimulation of dopamine-sensitive adenylate cyclase. The D₁ receptor class has been reclassified to include both types, with the classical D₁ receptor termed the D₁A receptor and D₅ termed D₁B.

The D₁A receptors are present in high concentrations in the caudate, putamen, nucleus accumbens,