

Parkinsonism and D-512, dopamine D2/3 receptor agonist; A review of literature

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Abstract

In 1817, James Parkinson first coined the term Paralysis Agitans (An Essay on the Shaking Palsy), Jean-Marie Charcot was the first to coin term Parkinson's disease (PD). Three most common and obvious symptoms in patients with PD are tremor, rigidity, and bradykinesia. A multidisciplinary team involving neurologists, primary care practitioners, nurses, physical therapists, social workers is used to diagnose PD. Nonpharmacological and pharmacological treatment is given to the patient. However, this disease demands more clinical translational and prognostic research, identifying biomarkers that can help in early diagnosis of the disease and on developing future disease-modifying interventions.

Keywords: parkinsonism; d-512, dopamine d2/3 receptor agonist

Introduction:

In 1817, James Parkinson first coined the term Paralysis Agitans (An Essay on the Shaking Palsy), Jean-Marie Charcot was the first to coin term Parkinson's disease (PD) [1]. PD can literally be termed as dopamine deficiency motor syndrome but non motor symptoms as malaise, weakness and increased sleep also occur. Levodopa a gold treatment for PD also targets the motor symptoms [2]. Non motor syndrome (NMS) refers to the non-motor symptoms occurring with PD. In 2000's NMS were studied and investigated [3]. NMS and its major impacts on quality of life in PD were thoroughly investigated and dire need for treatment schemes originated [4, 5] Braak et al. stated that pathophysiology of PD involves multiple neurotransmitters [6]. It is proposed that it is a prion like process with alpha synuclein lewy body deposition [7]. PD is multi system multiple neurotransmitter involving process [8, 9].

Incidence:

In United Kingdom 1/60 people may develop Parkinsonism and the incidence increases with age [10, 11].

Diagnosis:

The diagnosis of PD is challenging, structured clinical diagnosis and at times autopsies are needed to look for lewy bodies [12-15]. In Patients with PD the diagnosis may be missed in about a quarter of patients [16, 17]. Physicians usually look for signs and symptoms and if they are missing the diagnosis may go missed [18, 19].

Symptoms:

Three most common and obvious symptoms in patients with PD are tremor, rigidity, and bradykinesia. Tremor is the most common feature in

tremor predominant PD [20-31]. Postural instability also occurs along with neural degeneration in the hypothalamic brainstem or peripheral nervous system [32-35]. Micrographia and hypophonia are also associated with PD [36-38].

Treatment:

Patients with PD are treated for their motor as well as non-motor symptoms [39, 40]. Therapies are identified to lower the disease progression slowing the neural damage [41, 42]. A multidisciplinary team involving neurologists, primary care practitioners, nurses, physical therapists, social workers is used to diagnose PD. Nonpharmacological and pharmacological treatment is given to the patient. Jean-Martin Charcot and William Gowers were the first one to study Parkinsonism treatment. Treatment of Parkinsonian tremor with belladonna alkaloids was initiated [43]. They work by maintaining the cholinergic/dopaminergic balance in the striatum and thereby improve Parkinsonism. Tyler stated that Charcot was the first one to use hyoscyamine in its treatment [44]. Hornykiewicz made dopamine in the year 1910 [45]. Whereas P. Holtz discovered the enzyme, dopa decarboxylase and proved that levodopa was turned to dopamine by it. Hornykiewicz studies dopamine, adrenaline and noradrenaline and stated that dopamine was quite different from the other two. In the year 1950 dopamine was localized in the brain striatum and a model was made showing the use of levodopa. Hence emerging theories came to show that dopamine loss caused PD [46, 47]. Levodopa causes the motor symptoms to improve making the gait better even the articulation and speech [48]. Subsequently trials were done confirming the use of levodopa in PD [49-51]. Monoamine oxidase inhibitors and catechol-O-methyl transferase inhibitors were also discovered which acted as dopamine agonists. Amantadine was also discovered as an anti-Parkinsonian agent. It improves tremor and balance in PD patients [52] It causes inhibition of

striatal synaptic dopamine reuptake so dopamine level increases in the synaptic cleft.

D-512, dopamine D2/3 receptor agonist: The new trends involves treating PD with selective dopamine-D₂ and -D₃ receptor agonists though it plays no role in handicapping the disease progression. Researchers in US have discovered a new drug D-512, having increased affinity for dopamine-D₂ and -D₃ receptors with affect lasting thrice as long as ropinrole.

Antioxidant properties:

PD causes oxidative stress to damage brain tissue.D-512 has antioxidant properties [53].In an animal study, it was concluded that it carries a longer duration of action also helping in slowing disease progression. Also its antioxidant properties has a protective effect and decreases the oxidative stress in the brain [54].

Placebo:

Placebo-controlled trials also showed that placebo helped in treating PD [55]. The funding of federal grants for the specific study of placebo effects in Parkinson's disease is, in itself, of historical significance [56].

Conclusion:

Diagnosis of Parkinsonism disease is crucial and may at times go missed and at times it may overlap with dementia with Lewy bodies or Parkinsonian variants of multiple system atrophy. PD is a multisystem disorder. In time diagnosis and effective treatment can help slow and hamper disease progression improving the patient's outcome. However, this disease demands more clinical translational and prognostic research, identifying biomarkers that can help in early diagnosis of the disease and on developing future disease-modifying interventions.

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