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PRESCRIBING PATTERNS OF ANTI-PARKINSONISM DRUGS AND DEVELOPMENT OF TREATMENT OF DISEASE: A REVIEW

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ABSTRACT

Prescribing trends for medications are influenced by development of new drugs, changes in knowledge about efficacy and side effects, and priorities set by funding agencies. Antiparkinsonian agents are a group of drugs that are primarily used in the treatment of the neurodegenerative disorder, Parkinson's disease (PD). The most common antiparkinsonian agent used for the treatment of PD is levodopa, the precursor to dopamine. Other antiparkinsonian agents include dopamine receptor agonists, catechol-methyltransferase inhibitors(COMTIs), monoamineoxidase inhibitors(MAOIs), anticholinergics, and amantadine. Since prescribing trends for antiparkinsonism medications are influenced by development of new drugs and changes in knowledge about efficacy and side effects, few have focused on the utilization trends with either monotherapy or combination therapy in PD management The complications of long-term treatment with levodopa include-motor fluctuations, dyskinesias, and nonmotor fluctuations are such as mood disturbance, cognitive dysfunction, dysautonomia and pain. Till date, there are various therapeutic approaches having been developed for the treatment of advanced PD comprising Pharmacotherapy, neurotrophic factors, surgical procedures such as DBS, cell-based therapies and gene therapies. The main focus of this article is to understand the efficacy of prescribing patterns of anti-parkinsonism of drugs and development of treatment of disease.

KEYWORDS: Parkinsonism, S Tem-Cell Therapy, Gene Therapy, DBS, Neurotrophic Factors.

INTRODUCTION

Parkinson disease is a multisystem disorder, clinically characterized by motor and non-motor (NM) symptoms. The motor symptoms of PD include four cardinal features: bradykinesia, rest tremor, rigidity, postural instability and gait impairment.

1. Bradykinesia: refers to slowness of movements with a progressive loss of amplitude or speed during attempted rapid alternating movements of body segments.

2. Rest tremor (sometimes also called Parkinsonian tremor) is a rhythmic oscillatory involuntary movement that comes about when the affected body part is relaxed and supported by a surface, thus removing the action of gravitational forces.

3. Rigidity: refers to an increased muscle tone felt during examination by passive movement of the affected segment (limbs or neck), involving both flexor and extensor muscle groups.

4. Postural and gait impairment: Parkinsonian patients tend to adopt a stooped posture owing to the loss of postural reflexes, a major contributor to falls Non-motor (NM) symptoms, including autonomic disturbances (gastrointestinal, urogenital, cardiac, respiratory), sensory, skin, sleep, visual, neuropsychiatric dysfunctions (dementia, anxiety symptoms, depression, psychosis, impulse control disorders (ICDs), disorders of sleep wakefulness, apathy), olfactory dysfunction, and REM sleep behavior disorder (RBD), etc.[1] Antiparkinsonian agents are a group of drugs that are primarily used in the treatment of the neurodegenerative disorder, Parkinson's disease (PD). In PD the nigrostriatal dopamine pathway is severely compromised and the antiparkinsonian agents work to counter act the defective dopamine pathway or modulate supporting chemical pathways. Today there are no agents proven to slow the progression of PD. The antiparkinsonian agents are used for symptom relief and people with the disease face continual changes to their medication regimes to maintain optimal relief. The most common antiparkinsonian agent used for the treatment of PD is levodopa, the precursor to dopamine. Other antiparkinsonian agents include dopamine receptor agonists, catechol methyl transferase inhibitors (COMTIs), Monoamine oxidase Inhibitors (MAOIs), anticholinergics, and amantadine.[7] Changes in the rates

of utilization of each antiparkinsonian agent over time will reflect changes in the number of people taking the medication, changes in clinical practice, and medication availability. Such changes, however, might not bedue solely to their utilization in the treatment of PD. Despite being classified as antiparkinsonian agents, these drugs are also used for the treatment of other conditions. For example, levodopa can be used for the treatment of restless legs syndrome and gait apraxia, anti cholinergics are used for the treatment of extrapyramidal side effects of anti dopaminergic agents, dopamine agonists are used for the treatment of restless legs syndrome and to reduce prolactin secretion, and amantadine has also been used as an antiviral drug. The complications of long-term treatment with levodopa include-motor fluctuations, dyskinesias, and nonmotor fluctuations are such as mood disturbance, cognitive dysfunction, dysautonomia and pain.[10] Till date, there are various therapeutic approaches having been developed for the treatment of advanced PD comprising Pharmacotherapy, neurotrophic factors, surgical procedures such as DBS, cell-based therapies and gene therapies.[10]

Neurotrophic Factors

Neurotrophic factors (NTFs) or neurotrophins are endogenous proteins which are a subset of growth factors that play a pivotal role in the development, survival, differentiation and maintenance of specific neuronal cells in the developing and adult nervous systems that have the potential ability to protect degenerating dopamine neurons as well as promote regeneration of the nigrostriatal dopaminergic systems. The family of neurotrophins consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor GDNF, Vascular endothelial growth factor (VEGF), pigment epithelium-derived factor (PEDF), fibroblast growth factor (FGF), the cerebral dopamine neurotrophic factor (CDNF)/mesencephalic astrocyte-de- rived neurotrophic factor (MANF) family, the neurokines, neurturin, neurotrophin 3 (NT3), neurotrophin 4 (NT4), and neurotrophin 5 (NT5). Each binds to one member of the tyrosine receptor kinase (Trk) family: NGF binds to TrkA, BDNF and NT4 bind to TrkB, and NT3 binds to TrkC.[49]-[53] GDNF and neurturin (NTN) are the two main members of the family ligands (GFLs). GDNF signaling is mediated via a multicomponent receptor complex consisting of a binding receptor (GDNF family receptor alpha, GFRα) and a second receptor called Ret receptor tyrosine kinase.

6. Stem Cell Therapy

Over the past two decades, stem cell technologies have become an increasingly attractive therapeutic option to investigate and treat neurodegenerative diseases. Stem cells are divided into two groups: embryonic and adult stem cells. In another categorization stem cells are divided to Totipotent, Multipotent and Unipotentcells.[106] Naturally occurring stem cells generally include embryonic stem cells (ESCs), fetal stem cells (FSCs), and adult stem cells [107]. Various stem cell therapies are under investigations and have been developed to treat neurodegenerative diseases, among them embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), neural stem cells (NSCs) and induced pluripotent stem cells (iPSCs) are the most common tools that hold a great promise for regeneration of the brain.[108] Dopaminergic (DA) neurons in the substantia nigra pars compacta (also known as A9 DA neurons) are the specific cell type that is lost in PD. During neural development, A9 DA neurons originate from the floor plate (FP) precursors located at the ventral midline of the central nervous system which is essential for the embryonic DA neuron development.Stem cell-based therapies can be beneficial by acting through several mechanisms such as cell replacement, trophic actions, mediating remyelination and modulation of inflammation.

5. Deep Brain Stimulation

(DBS) Deep brain stimulation (DBS) has developed over the past two decades and still in developing phase as an effective therapeutic option for various neurological and psychiatric disorders. The Sub thalamic nucleus (STN), the internal segment of the Globus pallidus (Gpi), and thalamus are the standard DBS targets for the treatment of advanced Parkinson's disease, the tremor or rigidity and bradykinesia.[3] The Food and Drug Administration (FDA) has approved that DBS is safe, well tolerated, and effective for the treatment of advanced Parkinson's disease (PD), essential tremor (ET), obsessive compulsive disorder (OCD), and for dystonia. DBS involves the delivery of particular electrical signals to the specific deep anatomical structures of the central nervous system with the objective of altering or modulating neural functioning and achieving a reversible, adjustable and therapeutic or clinically beneficial effect. However, the exact mechanism of action of DBS is still under investigations, some authors suggested that DBS of the basal ganglia improves cortical function by alleviating excessive beta phase locking of motor cortex neurons.

METHODS

Data was collected from the outpatients in neurology and medical records department. Patient demography, disease duration, symptoms, co-morbid conditions, drug, dose, adverse drug reaction if any were noted. Information was collected again from the study participants during their routine follow up visit three months later to monitor the symptoms and adverse drug reactions (if any) occurring due to treatment. Causality assessment was done for the ADRs reported based on WHO scale.

CONCLUSION

In summary, till date, the treatment for PD remains essentially symptomatic although this approach is simple and effective during the early phases of the disease. The management of advanced PD is complicated due to the decline in the number of dopaminergic neurons, the development of motor complications, and the appearance

of non-dopaminergic motor and non-motor features, resulting in significant morbidity and a shortened lifespan. There are various therapeutic strategies have been advanced for the treatment of PD, including pharmacotherapy such as dopaminergic and non-dopaminergic therapies, anti-inflammatories, neurotrophic factors, DBS, cell based therapies and gene therapies. But all of these newer treatments have merits and demerits. Neurotropic factors are one particularly promising therapeutic and potentially neuroprotective approach. However, severe delivery obstacles have limited their application in PD treatment. Surgical treatment is becoming more common for PD because of advances in brain imaging and neurosurgical techniques. DBS of the sub thalamic nucleus effectively improves motor function and reduces motor fluctuations, dyskinesia, and antiparkinsonian medication effects, but the treatment is expensive, and cannot cure disease.

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