**Pathophysiology and Pharmacological Management of Parkinson’s Disease**

**Introduction**

Parkinson’s disease is caused by the gradual loss of cells in the substantia nigra region of the brain. This is the region that produces dopamine, the chemical messenger that transmits signals between the two regions of the brain to facilitate the coordination of activities. For example, dopamine connects the substantia nigra to the corpus striatum, which helps in regulation the activities of muscles. Therefore, if there is no enough dopamine in the striatium, the nerve cells of the region of the brain would be out of control. As such, the individual would be incapable of controlling movements of the muscles. Nevertheless, the exact cause of the loss of the cells, which finally leads to the manifestation of Parkinson’s disease, is unknown. Parkinson’s disease is thought to be caused by a combination of genetic and environmental factors. According to Cannon and Greenamyre (2013), the disease initially affects the dorsal mortal nucleus of the vagus nerve. It then affects the olfactory bulbs and nucleus. The locus coeruleus is the third part to be affected by the disease. The disease finally affects the sunstantia nigra, which leads to the manifestation of several symptoms associated with the disease. Damage to the cortical areas of the brain occurs at later as the disease progresses. The fact that Parkinson’s disease affects several neuronal systems leads to multifaceted pathophysiologic changes that make people with the disease have impairments to the motor system, cognitive system, and neuropsychological system (Kwan & Whitehill, 2011). This paper will discuss the pathophysiology of Parkinson’s disease and the pharmacological management of the disease in relation to its symptoms as manifested by Mr. Drew.

**Pathophysiology of Parkinson’s Disease**

The basal ganglia (BG), which includes the striatum, plays a major role in the motor function of an individual. The BG comprises of the putamen, nucleus accumbens, nucleus, global pallidus, substantia nigra, and the subthalamic nucleus (STN). The global pallidus is divided into the internal segment (GPi) and the external segment (GPe). The substantia nigra is divided into pars reticulate (SNr) and pars compacta (SNc) (Benazzouz et al., 2014).

The striatum, which receives inputs from various regions of the cerebral cortex, is the major input region of the BG. On the other hand, the GPi and SNr are the main output regions. The input and output regions are connected through pathways that arise from the matrix medium in the striatum that comprises of spiny neurons. The spiny neurons of the striosomal medium control the dopaminergic projections of the pars reticulate of the substantia nigra (SNr). The inhibitory gamma-aminobutryric acid (GABA) is the main neurotransmitter of BG’s circuit. On the other hand, excitatory glutamate is the neurotransmitter of the neurons of the STN. Dopamine is the neurotransmitter of the neurons of the pars compacta of the substantia nigra. This model asserts that the presence of indirect pathways that supersede direct pathways increase neuronal firing activity in the output of the BG, which leads to the manifestation of hypokinetic signs among people with Parkinson’s disease. The indirect pathways interfere with the normal speed of the movement that marks the onset and execution of movement (Olanow, Stocchi, & Lang, 2011). These pathways lead to abnormal activity of the motor loop of the basal ganglia.

The degeneration of dopaminergic SNc neurons and their subsequent projections to the striatum takes severa years. The SNc neurons that project to the putamen degenerate faster than limbic or associative sections of the striatum. The commencement of this form of degeneration leads to the development motor symptoms of the disease. The non-motor signs of the disease appear afer significant degeneration of the nigrostriatal neurons. According to Benazzouz et al. (2014), they occur after at least 70% of the cells have been affected. Loss of dopamine leads to several basal ganglia triggers. Reduction of the density of the dendritic spines of the MSNs is one of the morphological changes of Parkinson’s disease (Benazzouz et al., 2014).

Mr. Drew presented several signs and symptoms of Parkinson’s disease after being assessed by a general practitioner. They include “bradykinesia, gaze limitations (in all directions), a persistent unilateral tremor in his right arm, and a shuffling gait (with limited swing). His limb rigidity is ‘lead pipe rigidity’ but he also has cogwheel rigidity in his wrists” (Bullock & Hales, 2012, p. 188). In addition, Mr. Drew’s wife claims that he chocks and coughs frequently during meals. This is an indication that Mr. Drew also has dysphagia, which refers to difficulty in swallowing (Wellstead & Cloutier, 2012).

Bradykinesia refers to slow movement with ‘brady’ meaning movement whereas ‘kinesia’ relates to movement. Bradykinesia does not just lead to whole-body slowness. It may also impair fine motor movements of the affected individual. This is usually evident when people with the disease have to undertake rapid alternating movement of hand, fingers, or feet. In such a situation, they experience a progressive decrease in the speed and motion amplitude **(**Schulz-Schaeffer, 2015). Bradykinesia can also be exhibited cranially through lack of facial expression, reduced frequency of blinking, and decreased arm swing while walking.

Bradykinesia is one of the cardinal signs of Parkinson’s disease. However, its pathophysiology is not clearly understood. It is thought to be caused by the failure of the output of the basal ganglia (BG) to reinforce the cortical mechanisms that comprise of preparation of movement or the execution of the movement. Inadequate movement preparation among people with Parkinson’s disease is manifested by slower reaction times compared to other people. In addition, they have a slower increase in premovement cortical excitability. This implies that the stored motor commands of people with Parkinson’s disease have abnormal retrieval.

Mr. Drew also has a rigidity that occurs in the form of the lead-pipe rigidity of the arms and cogwheel rigidity in his wrists. According to Schulz-Schaeffer (2015), rigidity among people with Parkinson’s disease is greater in flexor muscles than extensor muscles. It is also more marked during slow stretching than in fast stretching. Cogwheel rigidity, such as the one Mr. Drew is experiencing, is caused by the presence of both rigidity and tremor.

MR. Drew was also diagnosed with rigidity. Rigidity is thought to be caused by changes in the passive mechanical properties of the tendons, joints, and muscles. It is also caused by the enhancement of stretch-evoked reflexes from the supraspinal or segmental spinal activity. Abnormalities in the peripheral sensory inputs of the brain may make the muscles stretch.

Dysphagia is also one of the signs of Parkinson’s disease in Mr. Drew. According to Suttrup and Warnecke (2016), 80% of people with Parkinson’s disease develop dysphagia. This leads to a reduced quality of life among patients of Parkinson’s disease since it makes it difficult for them to swallow medication. It also leads to malnutrition and aspiration pneumonia, which is one of the main causes of death among people with Parkinson’s disease. The pathophysiology of dysphagia is not clearly understood. However, it is thought to be caused by a defect in the cortical swallowing network’s dopaminergic and non-dopaminergic mechanisms. The involvement of the peripheral neuromuscular system is one of the major factors that lead to the multifactorial genesis of the dysphagia (Suttrup & Warnecke, 2016).

**Pharmacological Management of Parkinson’s Disease**

Management of Parkinson’s disease may be classified into pharmacologic, non-pharmacologic, and surgical therapy. The variety of pharmacological management of Parkinson’s disease is wider than any other degenerative disease of the central nervous system. Several factors should be considered during the pharmacological management of patients. These include the age, stage of the disease, the patient’s signs and symptoms, and level of functional disability. Parkinson’s disease is caused by the degeneration of the dopamine receptors and dopaminergic fibers. This leads to excessive muscarinic activity (Bullock & Manias, 2013). As such, pharmacological management of Parkinson’s disease involves trying to re-balance the dopaminergic nerve activity and muscarinic cholinergic activity. This may be undertaken using two methods, which include decreasing muscarinic activity or increasing dopaminergic activity. Preventing the breakdown of dopamine, stimulating the release of dopamine, and mimicking the actions of dopamine are also some of the pharmacological management strategies of Parkinson’s disease.

Antimuscarinic agents were the first compounds used in pharmacological management of Parkinson’s disease. Atropine was initially the main antimuscarinic agent used to treat the disease. However, several synthetic antimuscarinic agents have since been developed. It is vital to note than antimuscarinic agents cannot help in treating hypokinesia. However, they can be used to control rigidity and tremor associated with Parkinson’s disease. As such, antimuscarinic agents are only effective in the treatment of the early stages of Parkinson’s disease prior to the development of hypokinesia. Antimuscarinic agents inhibit the muscarinic receptors of the BG (Connolly & Lang, 2014). This helps in reducing the imbalance between the pyramidal and extrapyramidal pathways.

There are several antimuscarinic agents on the market. Some of the common agents include biperiden, benztropine, benzhexol, orphenadrine, and procyclidine. There are very small differences between these drugs. However, biperiden is slightly different from the other antimuscarinic agents. Biperiden has antinicotinic activity in addition to the antimuscarinic agent. As such, it may help in controlling muscle tremors. However, it is not as effective as neuromuscular blocking agents in blocking the tremors. Intake of benzhexol and procyclidine leads to euphoric symptoms, which is one of the main factors that have to the misuse of these drugs. Orphenadrine is highly effective in treating skeletal muscle pain and nocturnal cramps among people with Parkinson’s disease. Antimuscarinic agents should be withdrawn gradually after they have served in usefulness in pharmacology management of the disease. This helps in preventing the worsening of the symptoms of the disease (Bullock & Manias, 2013).

Increasing dopaminergic activity is the other pharmacological management strategy of Parkinson’s disease. Levodopa is one of the main drugs used to increase dopaminergic activity among patients of Parkinson’s disease. It is a globally-renowned drug for the treatment of the disease. Parkinson’s disease is caused by lack of dopamine activity in the substantia nigra. Levodopa acts as a source of dopamine. In so doing, it helps in increasing dopaminergic activity, which helps in treating Parkinson’s disease (Bullock & Manias, 2013). Levodopa should first be provided in large doses to ensure the right amount gets to the central nervous system prior to its conversion to dopamine. Carbidopa is also one of the drugs used in treating Parkinson’s disease. However, it should be used with Levodopa. Failure to which it would be ineffective. Cardibopa inhibits the peripheral metabolism of Levodopa, which increases its effectiveness in treating Parkinson’s disease.

The impact of levodopa in treating Parkinson’s disease usually reduces with time after continued use. After a certain period, the drug does not have any effect on patients of Parkinson’s disease. However, the drug becomes ineffective after several years of use.

Parkinson’s disease can also be treated by striving to prolong the activity of dopamine released from nigrostriatal nerves. This helps in countering the activity of muscarinic agents. Selegiline is one of the drugs used to prolong the activity of dopamine. Parkinson’s disease can also be treated using drugs that stimulate the release of dopamine. One such drug is amantadine, which was initially developed as an antiviral agent (Bohnen & Albin, 2011). There are also several drugs that can mimic the action of dopamine, which helps them treat Parkinson’s disease. Liruride, pergolide, and cabergoline are some of these drugs.

**Conclusion**

Understanding the pathophysiology of Parkinson’s disease would help in the development of treatment strategies for the disease. However, despite extensive research on the pathogenesis of the disease, it is still not yet clear what causes the disease. This is one of the main reasons as to why the drugs used to treat Parkinson’s disease are not as effective as the drugs of diseases whose pathogenesis is known. Therefore, more research on the disease should be undertaken by relevant professionals.

**References**

Benazzouz, A., Mamad, O., Abedi, P., Bouali-Benazzouz, R., & Chetrit, J. (2014). Involvement of dopamine loss in extrastriatal basal ganglia nuclei in the pathophysiology of Parkinson’s disease. *Frontiers in Aging Neuroscience, 6*, 87.

Bohnen, N. I. & Albin, R. L. (2011). The Cholinergic System and Parkinson Disease. *Behav Brain Res., 221*(2), 564-573.

Bullock, S. & Manias, E. (2013). *Fundamentals of pharmacology*. French Forest, N.S.W: Pearson Education.

Cannon, J. R. & Greenamyre, J. T. (2013). Gene-environment interactions in Parkinson’s disease: specific evidence in humans and mammalian models. *Neurobiol Dis., 1*, 1-18.

Connolly, B. S., & Lang, A. E. (2014). Pharmacological treatment of Parkinson disease: a review. *JAMA, 311*(16), 1670-1683.

Del Tredici, K., & Braak, H. (2016). Sporadic Parkinson's disease: development and distribution of α‐synuclein pathology. *Neuropathology and Applied Neurobiology, 42*(1), 33-50.

Kwan, L. C. & Whitehill, T. L. (2011). Perception of Speech by Individuals with Parkinson's Disease: A Review. *Parkinson’s Disease, 2011*, 1-11.

Olanow, C. W., Stocchi, F., & Lang, A. E. (2011). *Parkinson's Disease: Non-Motor and Non-Dopaminergic Features*. Hoboken, NJ: Wiley-Blackwell.

Schulz-Schaeffer, W. J. (2015). Is cell death primary or secondary in the pathophysiology of idiopathic Parkinson’s disease?. *Biomolecules, 5*(3), 1467-1479.

Suttrup, I., & Warnecke, T. (2016). Dysphagia in Parkinson's Disease: Pathophysiology, Diagnosis and Therapy. *Fortschritte der Neurologie-Psychiatrie, 84*, S18-23.

Wellstead, P. E., & Cloutier, M. (2012). *Systems biology of Parkinson's disease*. New York: Springer.