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Introduction

Parkinson ’s disease (PD) is a serious progressive disease that was first described in 1817 by James Parkinson. Many years passed before it was established that disappearance of doperminergic and non-doperminergic nerve cells in the substantia nigra of the mid brain was a primary feature in PD patients (Jankovic, 2008). This disappearance results the depletion of dopamine in the striatum. These nerve cells are responsible for controlling movement.

Statistics indicate that PD as a neurologenerative disorder in the United States is only superseded by the Alzheimer’s disease (Scott & Stacy, 2009). The mean age marking the onset of the disease is 57 year and it affects about 1 to 2% of the population above 60 years (LeWitt, 2008). The actual cause of the death of these cells to date remains unconfirmed. It has been suggested a number of contributing factors may include, genetic mutations, abnormal handling of some proteins by ubiquitin-proteasome and autophagy-lysosomal systems , mitochondrion dysfunction, inflammation , environmental factors, and other pathogenic mechanism (Jankovic, 2008). There are many forms of parkinsonian disorders categorized into four groups namely: primary (idiopathic)parkinsonism, secondary (acquired, symptomatic) parkinsonism heterodegenerative parkinsonism and the multiple system degeneration type(Jankovic, 2008).

PD impairs motor and non-motor function in patients predisposing them to significant physical, economic and emotional burdens that is manifested by disability, deficit in health-related quality of life (HRQOL), and increased risk

of early mortality (Scott & Stacy, 2009). This papers aims to deeply examine the present therapeutic interventions for Parkinson’s disease. In the first section, various aspects of cognitive, pharmacogical and alternative treatments for this disorder will be presented. The second part will try to relate the clinical manifestations of the disorder with the above treatments and a personal opinion for treatment will be offered. The last section before the conclusion covers contemporary attitudes towards the above treatments.

Therapeutic Interventions

To date, there are no known neuroprotective agents for PD. Although some agents have yielded promising neuroprotective effects in cell cultures and animals, their effects have been inconclusive in humans. In recent years PD therapy has focused on modifying disease progression other than controlling neurological symptoms (Scott & Stacy, 2009). Treatment for PD may involve pharmacological, functional surgery or rehabilitation procedures (physical therapy, speech therapy and Occupational therapy). Unlike surgery and alternative treatment, Most pharmacological interventions are designed to replenish and enhance delivery of dopamine to the affected areas of the brain . Because dopamine is unable to cross the blood brain barrier, pharmacological formulations use Levodopa , the precursor of dopamine.

The efficacy of levodopa has been established in the decades proceeding its first introduction in the 1960s (Oertel et al. 2011). The delivery of this precursor to the brain is made by coupling it to Dopa Decarboxylase inhibitors (DDI) such as Carbidopa or benserazide or Catechol-O-Methyltransferase (COMT)(e. g, Entacapone and Talcapone).

This coupling enhances the efficacy of levodopa by preventing its peripheral conversion and increases it bioavailability in the brain (Scott & Stacy, 2009). Over the years, Levodopa has become the preferred drug for the treatment of motor signs and symptoms of PD (LeWitt, 2008). Patients are known to recover from impairment of speech, gait and dexterity 15 to 30 minutes after administration of oral dose. For this reason, this response is also used as a confirmation criterion for proper diagnosis of PD (LeWitt, 2008). Both pharmacological and surgery (Deep Brain stimulation) have been shown to provide symptomatic benefits by reducing tremor , rigidity , stiffness and slowed movement (LeWitt, 2008).

However, most levodopa users experience motor complication with continued usage of the drug. This has been attributed to its direct neuromodulatory and neurotransmitter actions (LeWitt, 2008). Apart from pharmacological and surgical treatment many patients of PD also receive rehabilitation assistance in the course of the disease (Oertel et al., 2011). The efficacy of this therapy is not conclusive. The rehabilitation involves specialist drawn from the fields of occupational therapy, occupational therapy and speech-language therapy. These rehabilitations may be in form of monotherapy or as part of a team of approach (Oertel et.

al., 2011). They can also be engaged as part of adjunctive treatment with drug therapy or as mainstay treatment for symptoms that are resistant to other therapies (Oertel et. al., 2011). Physical therapy can reduce dependence on caregivers and improve the quality of life in PD patients by improving movement, enhancing function and lessening pain (Scott & Stacy, 2008) Physical therapy is limited in that can only address issues such as

balance, lack of coordination, fatigue, gait, immobility and weakness. It can also be used to develop exercise program for PD patients before motor problems arise. Recent studies have shown that exercise has a positive effect on motor sign and gait (Oertel et al.

, 2011). On the other hand, occupational therapy can help patients learn to perform mundane activities affected by the disease such as handwriting and use of various appliances. Emerging evidence has also shown that gait could be significantly improved through cued training , treadmill training in addition to cultural alternatives such as Tai Chi and Qijong (Oertel et al., 2011). Most drug therapies and surgical treatment are temporary although the later has been shown to produce much longer beneficial symptoms. The response to levodopa changes after two years and motor fluctuation and dyskinesias develop within 5 years of administration. To counter this effect, a combination therapy of levodopa and doperminergic agonists has been suggested in the initial treatment of PD (LeWitt, 2008). Another management alternative suggested involves delaying the introduction of levodopa in early PD when symptoms are mild and tolerable.

This strategy requires that levodopa be introduced only when the progression has reached levels of serious discomfort and disability (LeWitt , 2008). In the United States, levodopa administered together with AAD inhibitor, carbidopa on permilligram basis is efficacious Pharmacological therapy, just like surgical and rehabilitation procedures also involves a combination of an array of regimens for optimizing symptomatic relief (LeWitt, 2008). Adjunctive therapies are common features of parkinsonism (Oertel, 2011).

In stable PD, Efficacy for most drug agents is enhanced by supplementation with other medications (Oertel, 2011). For advanced PD, Levodopa may be combined with dopaminergic agonists, amantadine , MAO-B inhibitor or COMT inhibitor (LeWitt, 2008). Pharmacological therapy unlike surgery which is only a viable option in late PD, has been shown to be effective for early and advanced stages of PD. Drug therapy is the primary treatment for PD (Hayes Fung, Kimber, & O'Sullivan, 2010). Higher doses of Levodopa produce greater improvements but predisposes the patient to earlier ' wearing off'. Dopaminergic agonists are an alternative to levodopa as they do not produce motor fluctuation and dyskinesias .

However, they require augmentation with levodopa within two years to use to produce symptomatic improvement. Clinical trials have shown cholinesterase inhibitors produce beneficial improvement in cognitive and psychotic symptoms (Hayes et al., 2010).

Drug therapy for PD can also trigger of aggravate a range of neurophychiatric symptoms (Hayes et al., 2010). In such cases drug therapy using clozapine has been shown to reduce psychotic symptoms. Recidivism in more pronounced in drug therapies than in other interventions. Levodopa , administered thrice daily, offers symptomatic control throughout the day. However after years of treatment, motor complications typically, dyskinesias and motor fluctuations result. A meta- analysis by Oertel and colleagues (2011) found <40% likelihood or motor fluctuations and dyskinesias after 4-6 years of levodopa therapy. Surgical treatment may be considered when pharmacological intervention fails to slow down PD progression and severe motor fluctuations and dyskinesias persist.

In recent year Deep Brain Stimulation (DBS) has gained importance due to its beneficial effects in certain motor symptoms. According to Deuschl and fellow researchers (2006) the administration of continous electrical impulses to the subthalamic nucleus by a surgical implant has produced improvements in motor symptoms in advanced stages of PD . DBS appear to produce long lasting beneficial effects on motor symptoms such as tremor, bradykinesia and dyskinesias although its efficacy has not been conclusively established (Hayes et al.

, 2010). However, surgical treatments have not been shown to improve other symptoms such gait dysfunction and fall. In some cases some symptoms have worsened after the surgery (Hayes et al., 2010).

Common Symptoms and Management

Rest tremor, bradykinesia, rigidity and postural dysfunction are the primary motor signs of PD (Jankovic , 2008). These features indicate a positive diagnosis as they are unique from other related parkinsonian disorders.

Secondary motor symptoms include hympmimia, dysarthria, dysphagia, sialorrhoea, micrographia, shuffling gait, festination, freezing, dystonia and glabellar reflexes (Jankovic, 2008). Non motor symptoms are autonomic dysfunction, cognitive abnoramalities, sleep disorders and sensory disorders such as anosmia, parasthesias and pain (Jankovic, 2008). For brevity , the following sections only present the motor symptoms of PD.

This symptoms result primary from impairment of motor control and levodopa – dopeminergic agonist therapy usually are the first pharmacologicall intervention taken. Functional surgery and rehabilitation

therapy can also be considered when the drug therapies fail to control symptoms. Bradykinesia (slowness in movement) is a distinguishing clinical feature of PD and is said to be the hallmark of basal ganglia disorders (Jankovic , 2008). It features difficulties in planning, initiating and executing movement and with performing tasks that require fine motor control (Jankovic, 2008). It is also manifested by loss of spontaneous movements, drooling, dysarthria , impaired blinking ability and hypomimia (Jankovic, 2008). Rest tremor is also a prevalent symptom of PD. It mostly occurs at extremities but may also involve lips, chin, jaw and legs (Jankovic, 2008).

However proper diagnosis is essential to distinguish it from other forms of tremors such as Essential Tremors. Clinical pathological studies have shown that patients with PD have degeneration of a subgroup of mid-brain (A8) neurons (Jankovic, 2008). Though rarely used, clinical trial have indicated that Thalomotony may improve tremor (Oertel, 2011). Rigidity is characterized by increased resistance in movement of limbs and also in the neck, shoulders, wrists, ankles and hips.

In PD patient’s movement in these parts may be accompanied with pain (Jankovic, 2008). Rigidity of the neck and trunk may result in abnormal axial postures, Striatal limb deformities may also develop in some patients. Deformities of the hand are characterized by ulnar deviation, flexion of metacarpophalangeal joints and extension of the distal interphalangeal joints (Jankovic , 2008).

Foot deformities are characterized by extension of flexion of the toes. Postural instability occurs in advanced PD and is as a result of loss of

postural reflexes (Jankovicl, 2008). It is said to be the main contributing factor for falls and ensuing fractures (Jankovic, 2008). Other factors cited to influence postural instability in PD patients include: orthostatic hypotension, age related sensory changes and Kinesthesia (Jankovic, 2008). Treatment has involved doperminergic therapy and functional surgery (pallidotomy and Deep Brain Stimulation). However these interventions have been known to produce scant improvements (Jankovic, 2008). Physical therapy has also been cited as potentially effective in improving postural instability (Oertel et. al.

, 2011) Freezing is one of the most disabling clinical features of PD though its occurrence is not universal (Jankovic, 2008). It commonly affects legs and is characterized by inability to walk which normally occurs at the initiation of movement and during movement. It is a common cause of falls (Jankovic, 2008). The main subtypes of freezing are: start hesitation, turn hesitation, hesitation in tight quarters, destination hesitation and open space hesitation (Jankovic, 2008). It is mostly severe during OFF periods but can be subdued by levodopa therapy (Jankovic, 2008). It is more common in women than men. Risk factors for freezing include rigidity, bradykinesia, postural instability and generally advanced stage of PD. Rehabilitation therapy are mostly used to treat freezing due to its poor response to pharmacological therapies.

Cued training has been found to be effective in reducing the severity of freezing of gait (Oertel et. al., 2011). A reduction in dopeminergic therapy has been recommended for ON freezing although this strategy may negatively impact on “ wearing of” (Oertel et al., 2011).

Other pharmacological therapies for freezing include strategies such as adjustment of levodopa dose/formulation (standard and CR formulation), dopamine agonists and COMT/MOA-B inhibitors (Oertel et al., 2011).

Contemporary Attitudes Towards Treatment

The choice for a therapeutic intervention for PD is usually a subjective one (Rascol, Goetz, Koller, Poewe, & Sampaio, 2002,). Medical practitioners may base their selection on past experiences of a particular therapy.

Other noted considerations include age, perceived expectations, comorbidity, safety, efficacy, technical experience and cost (Rascol et al., 2002). In de novo patients there is always concern about how long to delay the introduction of levodopa for efficacy purposes and the long term motor complications that arise. In early PD characterized by absence of motor complications, adjunct therapy with relative safety implications is usually acceptable while in advanced PD patients, treatment decisions is normally based on the present motor fluctuations and dyskinesia (Rascol et al., 2002). It is common practice to delay non-pharmacological interventions; especially functional surgery unless motor complication failed response to drug therapies persists.

For surgical interventions such as DBS, application is only acceptable if the symptomatic benefits are considered greater than the nature of risks from surgery and that there is strong likelihood that the procedure will be more beneficial than convential drug therapies (Deuschl et al., 2006). Witt, Kutin, Timmermann, Zurowski and Woopen (2011) have also found out that the risk

of ‘ altered personality’ is especially alarming for patients, caregivers and clinicians.

Suggested Treatment

For early PD, I recommend a monotherapy of immediate or controlled releases of dopamine argonists (e. g pramipexole, piribedi, ropinirole) . These drugs have been found to be effective in early PD. Clinical trials data also indicate that there is low risk for developing complications with introductory dopamine argonist therapy (Oertel et al., 2011, p. 224).

Controlled Release (CR) Levodopa should only be introduced when motor symptoms have worsened to an extent of great discomfort and possible disability. This mode is based on clinical evidence that early usage of levodopa may contribute to early emergence of motor fluctuations and dyskinesias. Adjunct therapies of amantadine, COMT (entacapone only) and MAO-B inhibitors can also form part of the early interventions. Amantadine has been shown to induce symptomatic improvements while MAO-B inhibitors are well tolerated and have low daily doses.

For patients with persistent or emerging disabling tremor, DBS at the subthalamic nucleus can be considered. For advanced/late PD, I recommend a combination of immediate release levodopa with MAO-B and COMT Inhibitors. Levodopa has been established as the most effective treatment for motor fluctuations that is common during this stage.

The inhibitors serve to enhance the efficacy of levodopa. Another upside of levodopa is that it has also been shown to be effective in advanced PD patient with cognitive dysfunction in addition to possessing anti-hallucination

properties. For persistent dyskinesias, Amantadine can be used in addition to reducing the daily doses of levodopa and MAO-B/COMT inhibitors. Dopamine agonists can also be considered to compensate for reduce doses of levodopa. However, it adverse effects of inducing hallucination and psychosis should be noted.

For severe motor fluctuations DBS by stimulation of subthatllamic nucleus can be considered when drugs therapies have failed to contain it. Alongside medical and surgical interventions, rehabilitation therapies such as cognitive movement training and cued training are also advised. Late PD also present with a host of non-motor symptoms. The suggestion in this section is only for the motor symptoms which greatly impair the quality of life.

Conclusion

PD is a serious progressive disease that results in a much reduced quality of life in victims. To date the discovery for a neuroprotective agent for PD remains elusive. Current pharmacological therapies are the first line of intervention in initiation of treatment. However as the disease progresses, pharmacological agents lose their effectiveness.

Apart from their symptomatic benefits of therapeutic drugs for PD also produce an array of side effects hence necessitating a combination of different regiments. Clinical trials for modern surgical interventions such as Deep Brain Stimulation have produced positive results so far and their usage is gaining acceptance in many quarters. However the effects of such invasive procedures have not been well established. Rehabilitation measures can only

be used as supplementary therapy with surgical or pharmacological therapies.

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