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Education to Knowledge for your benefit

Foundations of Understanding Parkinson's Disease (IPD)

This handout has basic thoughts, ideas, and more complex considerations concerning IPD. Knowledge is power and power allows the patient with IPD and the family to have a better quality of life, activities of daily living, and a better journey with IPD. I will relate known data and thoughts about IPD and sometimes discuss theoretical ideas and issues that are often in debate. However the handout is for consideration and information and relates often discussed issues involving IPD and related diseases. However it is important to remember that IPD is a clinical diagnosis, it is a very heterogeneous clinical and pathological entity, that trying to subgroup these various phenotypes (different clinical pictures) is difficult if not impossible because of the lack of definite biomarkers, and that we treat patients with the idea of symptomatic improvement but there is no definite neuroprotective agents or disease modifiers.

There are three basic signs and symptoms of IPD. They are bradykinesia (slowness), rigidity (stiffness and tightness) and resting tremor. They are usually asymmetrical in IPD cases. Postural instability usually occurs later. Asymmetrical features are paramount as is an early absence of falling, dysphagia, cognitive impairment, significant orthostatic hypotension, anteflexion, retroflexion, early neurogenic bladder and hallucinations and delusions. Studies have shown that the best centers for Parkinsonism such as London Brain Bank's analysis early in the disease is only correct with early diagnosis in 50 to 75% of the time when compared with autopsies. This is similar to the diagnostic accuracy at five years in the Mayo studies by Dr Adler and others. Often on autopsies, there are multiple pathological diseases seen such as vascular disease, suggestive of cerebral vascular disease and beta amyloid abnormalities and tauopathy, suggestive of Alzheimer's disease (DAT). Later in the disease, the correct diagnosis when compared to autopsy is only about 85 to 95% correct. Those patients that have signs and symptoms other than typical or classical IPD are labeled by many as atypical Parkinsonism disease (APD). These diseases may fit into other disease's labeled such as multisystem atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), frontal temporal dementia cases (FTD), Lewy body disease (LBD), vascular disease, or combination of these or other significant comorbidities. There are now four signs or symptoms that may anticipate the diagnosis of IPD and help correctly diagnose the patient. These four symptoms may appear before other motor symptoms such as bradykinesia, rigidity and resting tremor. These non-motor signs and symptoms can occur and be associated with early or mid or late Parkinson's disease. These can be helpful in making and supporting the diagnosis. The four symptoms that are non-motor that may anticipate Parkinson's disease are depression, REM behavior disorder (RBD), anosmia (reduced or loss of smell) and constipation.

The diagnosis of IPD is still based on the clinical picture. Most of the clinical evidence is on the motor features. Bradykinesia is the foundation for the diagnosis. This is described as slowness of movement. 80 to 90 % of the IPD patients will have this at the time of diagnosis. It is usually distal, in the hands or arms and can be demonstrated by rapid movement of opening and closing of the fingers or hands and the patient notices reduced ability to do buttons, with also leg dragging, shuffling with short steps and the feet low off the ground and close together. Akinesia will be seen as slow to get out of a chair or car. Getting slowly out of a chair is a good test to do at home to monitor benefit of the medication. Gait freezing, festinating gait, and development of a more rapid short step gait that speeds forward with a flexed posture (running faster forward). Often bradykinesia is documented by doing rapid altering movement with the hands or finger that show reduction in speed, amplitude and breakup of the rhythm, all in varying degrees.

Tremor of the hand or arms (referred to as pill rolling) is the presenting symptom in 70 to 80 % of the patients with IPD. This occurs in a body part at rest and is reduced with purposeful activity (masking of the resting tremor. It is best seen with the hands at rest in the lap and is almost always asymmetrical. An action tremor can also be seen when a limb is used. A postural tremor is seen when the arms are held out in front of the patient. The postural tremor will start almost immediately. 20 to 30% of patients have an action or postural tremor but usually the resting is always more prominent or more severe. The re emergent tremor (postural) is a reliable sign that is named because when holding the arms out ward there is no initial tremor but upon waiting a few seconds a tremor occurs (re emergent). This supports IPD and indicates the need for starting or increasing L-dopa. Many IPD patients will describe early in the disease a tremulousness or internal tremor in the body more than the extremities. For the resting tremor, distracting such as counting or doing movements on the opposite extremity will make the tremor more prominent. This will also make the chin or tongue tremor worse and supports the diagnosis of IPD. Resting tremor seen when walking and which is usually asymmetrical maybe seen early and confirms or precedes the resting tremor in the hands which are resting in the lap. This however according to some may also be seen in essential tremor cases. Almost all IPD patients have resting tremor at some time in there disease journey. It usually starts in the hands, is unilateral and spreads to the other side but usually remains asymmetrical. The tremor is usually 3 to 7 per second but most is 4 to 5 per second. The tremor involves the hands, arms, legs, lips, jaw, tongue, but less the head.

Rigidity is the increase of tone or resistance to passive movement around a joint or in an extremity. Some describe it as a tightness. If similar movement of the opposite extremity is done the movement being tested will have an increase in resistance. This is call "augmentation". This maneuver done in the opposite extremity is helpful in bringing out subtle rigidity. 79 to 80% of IPD patients will have asymmetrical early or late rigidity often on the some side as the tremor, but not always. The term “cog wheeling" is a description of a racket like sensation when moving the extremity. The exact etiology of this phenomenon is uncertain and of great debate but most believe it is tremor added on to rigidity. Rigidity is often associated with pain, discomfort, stiffness and fatigue in the trunk, extremities, back and neck. A common sign for IPD is straightening of the interphalangeal joints with flexion of the Metacarpophalangeal joint.

Postural instability (PI) is in IPD a late clinical sign and is a state of imbalance and a tendency to fall. The "pull test" can be done by pulling back words or pushing forward on the patient. One step is normal but more than that is probably indicative of PI. PI is the least benefited by treating with L-Dopa or and medication. Physical therapy is the best form of benefit. DBS is also of little benefit and may be made worse by DBS. Some movement disorder specialist try to Sub Type the heterogeneity of parkinsonism into groups. One grouping is called Parkinson's Plus but I do not use that term. Others separate into 3 groups. 1) Tremor predominant, which is thought to be a slower, less progressive, slower to disability syndrome, and with less psychiatric symptoms. 2) Rigid-akinetic type with rigidity and akinesia as the predominate clinical features. 3) Postural instability-syndrome with early falling present. Many others use the term Atypical Parkinson Disease (APD) term is used by many and in lectures and movement publications when a definite subgroup is not present. A clear more definite reliable diagnosis in this disease with great heterogeneity is helped by some clinical features. One is a clear benefit from L-Dopa as compared to no response above the dose of 1000mg. If no response over 1000 mg of L-Dopa is documented, then often the diagnosis of APD is the best diagnosis. Supportive clinical features for IPD are clear, persistent benefit to L-Dopa, unequivocal "on" and "off", L-Dopa induced dyskinesias (how ever rarely patients with APD can have dyskinesias), persistent asymmetrical resting tremor, persistent asymmetry of rigidity and akinesia, olfactory loss, and later orthostatic hypotension (autonomic dysfunction early).

Red flags for the markers that the patient does not have IPD are many but not always so definite. Rapid gait impairment is key as are bulbar signs, speech, and swallow impairment. Inspiratory and respiratory dysfunction or stridor is seen in especially MSA. Severe autonomic failure in the first 5 years such as OH, and Neurogenic bladder as manifested by urge and or incontinence is seen early in MSA. Recurrent falls in the first 3 years indicates PI and APD. No progression of motor signs or symptoms after 5 years certainly suggests a patient that does not have a diagnosis of IPD. Antercollis, seen in usually MSA, as is contracture of the hand and or feet in the first 10 years. In a large meta-analysis (11 studies by Rizzo 2016) gives a diagnosis accuracy of 80% when

compared to pathological studies. There was 84% accuracy as compared to autopsy when last seen by a movement disorder specialist.

MRI has been of some additional help with the diagnostic accuracy. Using a 3.0 or 7.0 Tesla MRI can document the absence of dorso lateral nigral hyperintensity see in IPD patients. Its accuracy when compared to clinical and some autopsies studies suggest 85 to 90 % accuracy, however it is also abnormal in MSA, PSP, or LBD, but probably not VPD or drug induced parkinsonism. The DAT Scan, an isotope scan help with the diagnosis accuracy and has a accuracy of 85 to 90% but is not specially for IPD and can be positive in MSA, PSP, and LBD, but not in drug induced parkinsonism or unlikely in VPD. Patients with Scans without evidence of dopaminergic deficits are called SWEDD's. These patients infrequently develop classical IPD and their tremor is usually an upper extremity postural and kinetic tremor without other features of IPD. Some also go on to develop a genetic form of parkinsonism and they are a very heterogeneous group clinically. They may have bradykinesia with walking and reduced arm swing; some have facial dystonia, jaw and head and lip tremor, or adult onset myoclonus, but not the significant foundation of asymmetrical akinesia. A few after being observed for years will develop a slowly progressive Parkinson syndrome. Some will have a dystonic tremor that is thought to be a parkinson tremor. In the PRECEPT trial done for the new dug CEP-134 which was used as a new neuroprotective for IPD, there were 77 patients with SWEDD's, after 22 months 66 remained SWEDD's.

Myocardial scintigraphy is an isotope study that can document sympathetic denervation by having reduced uptake of the isotope in the myocardium. This is not commonly available nor is the newer test called trans cranial ultrasound, which on testing may show an area of hyper echogenicity of the substantia nigra but its reliability for diagnosis is uncertain, but some suggest up to 90% accuracy. Ultrasound ablation of the subthalamic nucleus is also being done in some hospitals but it is an ablation, which has many disadvantages. Olfactory dysfunction is considered to be common in patients with IPD and can be easily tested and suggests IPD in about 90% of the cases of IPD. Olfactory loss is uncommon in patients in CBS, FTD, PSP and ET. Serial exams and careful monitoring often results to an accurate diagnosis for IPD. ET occurs in 5% of population, in 70 to 80 % have a positive family history and it is usually an action tremor. Some IPD patients have a postural and or an action tremor, yet the resting tremor is usually more prominent and will have also have a "Re emergent" tremor that supports the diagnosis of IPD.

There are a number of genetic mutation syndromes that are of interest clinically and yet are rare. Here are discussed some genetic clinical syndromes that have parkinson clinical features that have been described over the last few years. The Parkin mutation in hemi parkinsonism hemi atrophy (HPHA), which clinically has associated one sided parkinson features and significant limb atrophy. The DJ-1 (Park7) is less frequent that Parkin (Park2). In these syndromes the clinical picture may be responsive to DBS. Park is associated with the most common identified cause of recessively inherited Early Onset Parkinson's Disease (EDPD) and is associated with 77% of juvenile or young Parkinson syndromes. DJ-1 and Parkin is seen as a recessively inherited parkinsonism. Rapid Onset Dystonia Parkinson (RODP) is an autosomal dominant movement disorder and associated with sudden onset oral facial dystonia, dysarthria, dysphagia and dystonic spasms in the upper extremities is associated with akinesia, rigidity and postural instability and associated with DT12 region described as ATP1A3. Monogenic forms account for 20 to 30% of early onset PD. and 3 to 5% of the sporadic forms and are Parkin, Pink1 (PTEN-induced putative Kinase 1), DJ1, and LRRK2. In these genetic syndromes the non-motor signs and symptoms are less prominent than in IPD. Another genetic form of parkinsonism is Dopa Responsive Dystonia (DRD).

Proteasomal function alteration may play an important role in the protein alpha synuclein accumulation. Its role in development of Lewy Body formation and aggregation and neuronal death. The cause of Proteasomal dysfunction is unknown, but gene mutations, oxidative stress with damage, ATP depletion or environmental toxin or any combination of all probably plays a role.

Death of dopamine neurons occur most likely from 1) aggregation of abnormal alpha synuclein, 2) oxidative stress 3) and genetic influences as a factor also. Certain gene mutations have certain influences. The DJ-1 and the PINK1 brings about loss of neuroprotective function. Also alpha synuclein and LRRK 2 both bring about a

gain of toxic function. It is thought that alpha synuclein has a fibril formation and the formation goes from dimers, oligomers and protofibrils.. The oligomers are thought to be the most toxic and the aggregation destroys (is toxic to the cell)and the spreads. Stabilizing the Nrf2 (nuclear factor erythroid 2 related factors) may be of benefit. GWAS (Genome -wide association studies) usually are used to assess the allele status and compare base pairs in affected and unaffected individuals. The SNP's (single nucleotide polymorphisms) are studied and focusing on SNP's located in coding parts of the genome or exome, gives new information. In DAT there has been found 2 loci , DYSF, PAXIP1 and as usual APOE on Chromosome 19. Using microarray analysis to capture rare exome SNP's gives greater insight into genetic and maybe clinical and treatment concepts.

Genetic influences (mutations), play an important role in the younger parkinson patients and is influential in 10% or more the cases of IPD. SNCA, alpha synuclein, UCIHL1, PINK2, LRRK2, VPS35, Parkin 1, DJ-1 ,GBA, PARK 1-13 are known gene mutations. With genetic mutations there may be also a decrease in Proteasomal and Lysomal function. Hence Proteasomal dysfunction is possibly a key factor, with possibly other influences that are involved in the path of events in the pathology dysfunction of one or both may affect the clearance of ubiquitinated and non ubiquitinated proteins. The clearing may also be related to so much aggregated protein present that it cannot be cleared. The pathological criteria for IPD is still being discussed and is challenging as an arbiter of the diagnosis of IPD. There are many reasons for this dispute, one is that the pathological picture does not always fit the clinical findings and there is also often more than one pathological type seen in autopsies of patients with IPD. Also there are genetic causes without alpha synuclein deposits. Also there are many cases of incidental Lewy Body deposits found in patients without parkinson findings. Hence the concept of the stages or phases of IPD, Pre symptomatic, Non motor, and Motor phases.

Genetics as an etiology, now with many more genes known, (and more being discovered),are grouped as to effect as 1) causative, or 2) associated or 3)influencing with Parkinson's disease may help with the diagnosis. However, one gene may give many different clinical symptoms or many clinical pictures (different phenotypes or many different clinical features are seen from one gene. And a similar clinical picture (phenotype) may be seen associated with many different genes. LRRK2 may account for 5% of the sporadic cases of IPD and 10% of the familial cases. LRRK2 is often seen in the AJ population. The glucocerebrosidase gene (GBA) is probably the most common genetic cause associated with IPD. It is linked to Gaucher disease and is being investigated now since it is thought that this mutation accounts for 5% to 15% of IPD cases or is related to this mutation, often ethnically related. The GBA mutation is thought to reduce the activity of the glucocerebrosidase (GCase) protein. Hence counteracting the mutation could lower the progression of the disease. Hence, some of the newest research and efforts are being made to document this mechanism, clinical picture and the pathology.

Gene therapy for IPD is considered to be of 3 types. All use the adeno-associated virus with type 2 serotype, AAV2.There has been many rodent and primate species used to evaluate gene therapy. It is thought that there is no need for a regulator promoter. The pathology of Parkinson disease is in the brain, spinal cord, autonomic system, salivary glands and even the skin. The concept of gene therapy is to restore dopaminergic function. The 3 types are as follows. The first one is gene delivery of dopamine synthesizing enzyme aromatic amino acid decarboxylase (AADC) to the striatum, using the adeno associated virus. This theoretically will bring about the over express of the AADC. Hence giving a more constant and physiological striatal dopamine. The second gene therapy is using the AAV2 vector to deliver glutamine acid de carboxylase (GAD) to the subthalamic nucleus (STN). This is thought to reduce the over activity of the STN, like what is thought happens in part with DBS. The third type of gene therapy is using AAV2 neurtuin (Cere 120) , a trophic factor put in the putamen and the trial used a Sham arm. Neurtuin is thought to augment dopamine biosynthesis and protect the existing neurons. The studies where positive in rodents. The initial trial in humans failed the primary end point at 12 months but suggested benefit at 18 months and some second end points at 12 and18 month were considered positive. Hence neurtuin or Cere120 does not have a double blind positive result. Now a human trial is putting neurtuin in the SN and the putamen and it appears that it is feasible and safe and the study is now 2 or more years in duration and showing acceptable safety data and fits with Class IV evidence. Again, like stem cells, using AAV2 is suggesting that there is no known cure for IPD.

There is now a reconsideration of the role of immunology in the role of the pathology of Parkinson's disease. Age is the greatest risk factor for Parkinson's disease, and since immunosenescense is a known factor in the health of individuals .The loss of immunological capacitity may play a role as it has been shown in other diseases. But it is also know that immunology may play another role. The alpha synuclein gene produces a protein that can and does in Parkinson's disease accumulate inside neurons. Misfolded alpha synuclein can trigger an immune response and T cells become activated with exposure to alpha synuclein and hence the T cells could play a role in the Pathophysiology of Parkinson's disease as they do in other diseases. An example would be a sequence and process that occurs in MS (multiple sclerosis), where an antigen activates the T cells and a sequence of events occurs that beings about loss of myelin, axonal loss and production of toxic cytokines. This is being studied in Parkinson animal models and in serum of Parkinson patients. Also inflammation may play a role in the pathology.

Most movement disorder specialist do not believe that stem cells research will lead to a cure for IPD. There are efforts to move this science forward; however the Lewy bodies are known to occupy the implanted stem cells, hence showing evidence of the continued spread of the alpha synuclein. And two human clinical trials showed no clinical benefit and some patients had severe movement that were noted as a severe adverse effect. But it is known that reducing comorbidity (vascular disease, diabetes, hypertension, pulmonary disease and renal disease) certainly may avoid some of the medical problems later in the in the IPD journey. The only known way to delay the progression of the disease at this time is through aggressive exercise (high-capacity exercise), increasing the heart rate to 60 to 80% maximum heart rate, one hour a day for 5 days seems to be the general concept. There are other exercise programs such as Tango dancing that improve the clinical picture and may reduce the progression of IPD. Two new diagnostic tests may help with the accuracy of determining dopamine deficiency and or dopamine dysfunction in patients, and may strongly support the diagnosis of IPD. Both support the reduction of dopamine in different parts of the substantia nigra neurons (presynaptic). These cells are the origin of the neurotransmitter dopamine that is deficient is IPD and some other APD's. The DAT scan which uses an isotope documents the presence or reduction of the presynaptic distal neuron's dopamine transporter function and hence when reduced, supports the reduction of the dopamine cells or their dysfunction in delivering the dopamine as a messenger to the postsynaptic cells in the putamen and caudate. Studies support the correlation with the diagnosis of IPD, but the reduction is also seen in the APD cases and LBD. Autopsy studies for the test's accuracy (sensitivity and specificity) in IPD have however been few. A DAT Scan quantitive analysis is now available however. Its benefit over just the appearance (visual estimate) on the scan is still uncertain. The accuracy of this DAT Scan for IPD seems to have a sensitivity and specificity of about 85 to 90%. Using a 3 Tesla MRI now can determine a high signal on the MRI in the posterior third of the substantia nigra nucleus and this is thought to represent clustered dopaminergic nigrosome cells which support a functional dopamine cellular area. The presence of this MRI finding (called the "swallow sign") is a negative predictive for the IPD. The sensitivity and specificity with clinical case correlation is about 85 to 90%. The significance of this is uncertain in APD and LBD and clinical studies and autopsies comparisons are yet to be determined. In my experience this MRI finding is robustly correlative to the clinical picture of IPD.

Early treatment for IPD often is with the use of an MAO-type B inhibitors (Eldepryl, Selegiline, Azilect and the new Xadago) and probably also amantadine chloride may well be of some benefit. Anticholinergics are used for tremor, usually only in the younger and early in the course. They are avoided in the cognitively impaired and older patients, those with co morbidity. Later dopamine agonist (pramipexole, ropinirole, and the patch, rotigotine) are used to improve the signs and symptoms. They can be used as monotherapy, with MAO-type B inhibitors, and most often L-Dopa is used as an adjunctive therapy. L-Dopa may be used first and then a dopamine agonist added. Dopamine agonist especially in older patients are likely to have significant adverse side effects including fatigue, drowsiness, ankle edema and redness, orthostatic hypotension (becoming clinically obvious or worse), impulsive-compulsive behavior (ICB), cognitive impairment, hallucinations and or delusions. A dysfunctional dopamine syndrome (DDS), is where the patient is constantly increasing the dopamine agonist (or L-dopa) in an addictive-like fashion. This is often difficult to correctly diagnosis since the patient may be trying to reduce "off" time, or suboptimal therapy. The drug should be slowly reduced and not stopped suddenly because of a possible resultant Neuro Malignant Syndrome or Serotonin Syndrome. Another dopamine agonist is Apomorphine or Apokyn that is used as a subq injection that can be used at various doses

and can reduce "off" time, EDF, morning "off" and as a rescue drug when the other medications are not effective. Sometimes it is used to test for dopamine responsiveness. Doses from 2mg to 8 mg can be used with each injection and as many as 5 injection can be used a day. It has its onset of action in 7 to 20 minutes and the effect lasts 60 to 90 minutes. Adverse effects are nausea, yawning, drowsiness, orthostatic hypotension, and dyskinesia. Apomorphine can be very helpful in improving motor activity when needed or other "off" symptoms.

L-dopa is the gold standard in the treatment of Parkinson's disease. L-dopa, the most effective drug for IPD, is used when a robust effect is needed and is used often after the disease has progressed. Most often this therapy is used when there is need to improve ADL and QOL that has not been ideal enough for job function. Hence, non L-Dopa therapy has not been enough. The carbidopa/L-dopa is known to be in various forms. It comes as immediate release (IR), is seen as Sinemet CR, Stalevo (with entacapone) and a new formulation release L-dopa (Rytary) and probably later other L-dopa forms (inhaled, sublingual, and patch forms). Rytary has been a major benefit for many of my patients in my office. Since it has a 4 to 5 hour constant plasma life it has been easily adjusted to reduce the "off" time, end dose failure(EDF), and even dyskinesias, when carefully titrated and adjusted. It certainly has reduced or delayed the use of DBS in my practice. Some of the patients on L-dopa can also have ICB or a dysfunctional dopamine rewarding syndrome. It can have side effects of nausea, vomiting, drowsiness, dizziness, orthostatic hypotension, dizziness, dyskinesia's, hallucinations and delusions plus other less common ones such as the urine turning brown.

Red flags for other diagnoses such as APD (Atypical Parkinson's Disease) are helpful in making a diagnosis other than IPD. The red flags are an early, more rapid progressive journey with the symptoms, early onset gait difficulties and more frequent falls, balance difficulty (ataxia), dysphasia, dysarthria, dementia, ante flexion, retro flexion, and neuropsychiatric manifestations (delusions and hallucinations). These are some of the signs and symptoms that suggest APD. A more rapid downhill course, and minimal or no response to L-dopa, strongly supports a more likely diagnosis of APD. As mentioned, these APD clinical cases have very heterogeneous clinical diagnoses. They are MSA, PSP, CBS, FTD and LBD, but often it is very difficult especially early in the journey to accurately be certain of one of these diagnosis, and clinical autopsy correlation studies bear this out. As of yet there is no marker or makers that can make these exact diagnoses. LBD is definitely a spectrum or heterogeneous disease with Lewy body pathology being seen on autopsy at various stages with a temporal (time) and geographic (location anatomically) spread of the pathology. LBD has early dementia with Parkinsonism and has significant difficulty with inappropriate somnolence, loss of attention, loss of focusing and with vivid visual hallucinations. Autopsy is the only absolute way to make the diagnosis in these neurodegenerative diseases. Studies have shown when comparing clinical diagnosis with autopsy findings, there is often an error rate of as high as 40%. Many of the autopsies have multiple different pathological findings that are consistent with Alzheimer's, vascular disease, frontal temporal dementia and other APD pathology and even now more cases with amyloid angiopathy with micro hemorrhages. One very interesting broad clinical spectrum disorder is Fragile X Syndrome. There is an abnormality in the "X" chromosome and the syndrome is seen more in males than females, and children have many different clinical features with autism like features (learning and behavior problems) and developmental delay. But in older males there is a clinical picture that has ataxia tremor, peripheral neuropathy and dementia and can look like a Parkinson syndrome. There is now a blood test for the fragile X Syndrome.

Lewy Body Dementia (LBD) is the second most common cause of dementia. Most likely, other that the very classical presentation in the first year, which is that of hallucinations (usually vivid visual, well formed and detailed), fluctuating cognition with pronounce variation in attention and alertness, and RBD, it is a spectrum disease and difficult to be certain of the diagnosis, especially from IPD with Dementia. These are the early clinical features. Also early clinical features are periods of somnolence during the day, and various features of parkinsonism (at least one with bradykinesia, then rigidity and less frequently resting tremor). A diagnosis of LBD is a spectrum clinical picture. It is difficult to differentiate from IPD with dementia where the dementia occurs later in the IPD. LBD often has severe sensitivity to Neuroleptics, autonomic dysfunction, postural instability, falls, periods of unresponsiveness, delusions, apathy, and depression. The differentiation between PPD and LBD is arbitrary and the 1 year rule in uncertain since the Lewy body pathology has a heterogeneous

pattern of it temporal and geographical spread. In autopsy studied cases the most common error in diagnosis is that cases that were LBD patients were mistakenly diagnosed as DAT.

Multiple System Atrophy's (MSA) clinical picture is in most patients (and thought to be the classical presentation) that of dysautonomia, cerebellar involvement, pyramidal signs (spasticity, hyperreflexia) ,symmetry, and a poor response to L-Dopa (weak initially and not robust). Cognitive loss is mild, but strider, ant flexion and early falling is common early. The alpha synuclein aggregation occurs but is in the oligodendrocytes rather than in the neurons.

Corticobasal Syndrome (previously called Corticobasal Dementia) is a progressive asymmetrical (alien limb syndrome) with akinesia, rigidity, dystonia commonly, with focal myoclonus, apraxia, aphasia, behavior changes and visual spacial deficits. Cognitive impairment is early or late and there is no response to L-dopa. Progressive Supranuclear Palsy (PSP) often has early, often first gait disturbances with falls. Supranuclear palsy is present at some time, not always early and occurs first vertically. Dysarthria, dysphagia, rigidity and frontal cognitive and behavior changes are seen. Different phenotypes are attempted to classify some of the patients into groups, such as the PSP parkinson group or the cerebellar group or the frontal temporal group. Some of these cases will have an anterior cell involvement with motor weakness and facilitations (ALS like picture). Basal ganglia calcifications can be seen as an idiopathic or a familial entity (Fahr's syndrome). The calcifications are best seen on CAT Scans but also can be seen on MRI's. For a clinical picture these patients often have onset of the disease from 20 to 60 years of age and have clinically a picture of various basal ganglia features with rigidity, akinesia, chorea, dystonia, cognitive changes and ataxia. The familial cases have a Autosomal dominant picture, and multiple gene mutations are found. These cases are not related to hypo parathyroidism or pseudo hypoparathyroidism. Non specific calcification on CAT scans can occur and are present in 1% of the CAT scans done. Other clinical diseases need to be considered in the differential diagnosis such a Wilson's disease (a cooper metabolism disease), ferrinopathies, and Spinocerebellar syndromes, and paraneoplastic syndromes.

Secondary Parkinson's disease has many etiologies. Drugs such metoclopramide (Reglan), anti-psychiatric drugs (prochlorperazine, reserpine and many others), some anti depression, anti anxiety drugs, and anti emetics are some of the causes. Clinical the picture is that of rigidity, akinesia, akathesia, a tardive chorea or dystonia, and the tremor, which is usually postural and action and less commonly a resting tremor that may even be asymmetrical. Other toxins such as carbon disulfide , carbon monoxide, MPTP, manganese and possibly some organic solvents may give a parkinsonian clinical picture. CHI or closed head injury and Cerebral Traumatic Encephalopathy (CTE) maybe associated with parkinsonism. The Sun City study in Arizona documented that CHI was a risk factor of Parkinson's Disease. Structural lesion such a SDH's, stroke (especially lacunar strokes) and WMD may have parkinson features. The diagnosis of Normal Pressure Hydrocephalus (NPH) has great controversy and even the clinical features are uncertain and are seen in many other diseases but it is reported to have some parkinson features. Huntington's, an autosomal dominate disease can present with parkinsonism, but has a genetic marker. How to make a diagnosis of NPH and determine shunt responsiveness is known. Vascular Parkinson's is fairly common by itself and as a comorbidity with Parkinson's Disease. Metabolic diseases such as Wilson's disease, hyper parathyroid disease, liver failure, and neurodegeneration with iron accumulation have parkinson clinical features as does neuroacanthocytosis, Celica's disease and Whipple's disease. The classical infection(viral) in the early 1900's that had parkinsonism was Encephalitis lethargic or Von Economo's encephalitis. Also HIV, Neurosyphilis, prion disease, PML, toxoplasmosis and many other viral or fungal infectious diseases may be associated with parkinson clinical features.

The clinical picture of neuropsychiatric (NP) features when present in Parkinson's disease, needs to be managed. A logical algorithm of reducing medications needs to be established. A major issue or concern is tapering off a clinically beneficial drug to a lower dose and trying to minimise symptoms, but yet when this is done, the patient's clinical motor and non-motor symptoms may get worse. Hence a thoughtful hierarchy of discontinuing various drugs should be established, going slow with reduction of one of the drugs at a time. Usually withdrawal of anticholinergics first is a common approach, then probably amantadine and next MAO-type B inhibitors, and then dopamine agonists. Because of this complexity, it is often beneficial to try to reduce

the number of drugs a patient is on in the therapeutic journey. It is difficult sometimes in reducing L-dopa because the benefits of L-dopa for bradykinesia, rigidity, and tremor are fairly robust and when reducing the L-dopa, there maybe improvements in some of side effects (NP), or specially rewarding, or dysfunctional dopaminergic use, but the patient may significantly worsen their bradykinesia, rigidity, tremor, and hence reduce their activities of daily living and quality of life. Hence, great care needs to be taken in establishing these decisions. Nuplazid (pimavanserin) has been of great benefit in reducing the hallucinations and delusions of various types and is much more effective than has been quetiapine (Seroquel). Side effects for Nuplazid are nausea, confusion, hallucinations, balance difficulty, constipation, extremity edema, and concern for QT interval prolongation. The dose is two 17mg pills at night. Often for agitation, and other behavior issues, quetiapine needs to be continued or added to allow management of the patient. There are no major studies using these two drugs in comparison or together. Adverse side effects for quetiapine need to be careful monitored, especially the cardiac issues, ie the QT interval prolongation ,sedation, seizures and worsening NP symptoms. Quetiapine has many listed adverse effects, which are listed as increased mortality, CV events, Neuroleptic Malignant Syndrome, tardive dyskinesias, seizures and lowered blood counts.

In maintaining benefits, especially L-dopa, one must know the motor and non-motor signs and symptoms and if they are present early or later in the disease or if they occur with wearing off or when the dose is missed or not given. This is crucial information in managing the patient's pharmacological journey. Individualized treatment in non-pharmacological and/or pharmacological therapy requires a good understanding and knowledge of all IPD signs and symptoms by the patient, their family and caregivers. Hence, education of the patient and the family and caregivers is paramount. Heterogeneity in these diseases clinically is significant and everyone has their own disease and hence need individualized pharmacological treatment depending not only on their signs and symptoms, but also on their age and comorbidity.

A new formulation of amantadine(GoCovri), extended release capsules, is being released and is being used for treating dyskinesias in patients on L-dopa. The first week a 137mg capsule is given at night and then two of the 137 capsules are given. If the drug is going to be stopped, the dose should be reduced by half for one week and then stopped. The clinical trials show reduction in dyskinesias and also document improvement of "off" time by one hour. It is a once a day, at night, dosing and will be of benefit for reducing dyskinesias and may well delay the use of DBS. The maximum plasma level is obtained early in the next morning. Adverse side effects are drowsiness, somnolence, hallucinations and delusions dizziness, orthostatic hypotension, dizziness, and confusion. Xadago,or (safinamide), a new MAO-type B inhibitor has also been released for the treatment of Parkinson's disease and improves "off" time by about one hour and improves the UPDRS and gives clinical global improvement. Dosing is 50mg for 2 weeks then 100mg. Side effects are nausea, dizziness, drowsiness, difficulty sleeping and some other side effects.

Exercise is a treatment format for IPD and probably any Neurodegenerative disease. Various exercise programs have been used to improve balance, strength and avoid falling. Patients with IPD have a 3 fold increase in falls and about 20 to 30% will die in one year, if they fall and many do not get out of a wheel chair or bed. Exercises reduces fatigue and pain with rigidity. Music therapy, massage therapy, and dance especially Tango, Tai Chi, and Rock boxing, all are probably of benefit, but large clinical controlled trials with placebo are lacking. But generally 1 hour at 60 to 80% of maximum heart rate is probably shown to be of benefit. Liu has reviewed endurance exercise and the benefits and changes depend on the intensity and duration. The changes that are thought to occur are 1) immunoprotective, which are listed as better able to fight infections, better wound healing and better vaccination response, 2) immunopathological improved response ie. better autoimmune response, 3)better immunoregulatory inhibition response or greater anti inflammatory capacity, 4)changes in microarray analysis, 5)higher leukocyte protein production and greater mitochondria biogenesis, and 6)down regulation of inflammation.

Much has been studied and undertook about aging, the physical and cognitive changes in an individual and DiBenidetto has reviewed this recently. Aging is associated with low grade inflammation in the immunological and CNS systems. There is definite immunosenescense, (loss of immunological capacity with aging), which is associated with low grade inflammation generally. An adult does have the capacity for neurogenesis, in many

systems including the CNS (Dr Rusty Gage at Salk's).Neuroplasticity and neuro remodeling does occur and new synapses are formed and changed and new neurons can be developed. Peripheral lymphatic systems and CNS communicate and are adaptive. Factors that play a role in body changes are aging, environment ,genetics and local metabolic activity. Physical activity slows down cognitive impairment and maintains cells, synaptic sites and specifically maintains hippocampal volume.

It is very important that the patient and family understands motor and non-motor symptoms either early or in the disease progression. Most importantly, understanding wearing "off" or "end-dose failure" in the treatment format. Motor wearing "off" symptoms are bradykinesia, difficulty getting out of a chair, slowness with walking, dystonia, imbalance, unsteadiness, muscle cramping, "off" dystonia, reduced dexterity, loss of fine motor activity, morning "off" or slowness in the morning or during the night as noted by inability to roll over in bed, stiffness and soreness, tremor,(primarily resting tremor), and generalized weakness and fatigue. Patients must know the difference between tremor and dyskinesias. To see examples of dyskinesias of various forms and severity and anatomical locations, Google one of Parkinson's best friends, Michael J Fox in some of his interviews.

Non-motor signs and symptoms of wearing "off" or symptoms and signs seen in early disease are abdominal discomfort, akathesia (uncontrollable motor restlessness), anxiety, depression, foggy or cloudy thinking, dullness of thinking or slowness of thinking, sweats (occurring during the day or at night", drooling, (first seen at night on the pillow then later seen during the day), dysphagia, dyspnea or shortness of breath, fascial flushing, double vision, fatigue, irritability, mood changes, (anxiety, variable depression), numbness, pain (in various parts of the body), dystonia or tightening sensations such as in muscles and tingling sensations. These can be grouped into 3 groups. These groups are autonomic, cognitive/Psychiatric and Sensory.

My approach is that helping people and others in the world should be our goal and taking our time, knowledge and ability to make a difference for our patients. In other words, giving back. The patient and the family need to know their disease, their signs and their symptoms and their own individual needs, so everyone will be best able to fit their care and therapy to their best quality of life and activities of daily living. But also for the their families and caregivers the best quality of life with reduction of caregiver burden which a significant but often ignored issue. We all need passion, persistence ,inspiration and resilience and we can improve any and every journey.

For resilience we need a support group, friends and need to make connections. Know that the journey of life and of aging and diseases involves changes and the changes we must work with and do not see them as impossible , unable to master, or adjust to modify. Focus on the event, problem and issue and solve one at a time but take definite, obvious determined effort and actions. Be positive and surround yourself with positive people. Be realistic, think of all possibilities and recognize realistically where you are currently. Have quiet time, mediate if possible, pray often if you pray, and spend quality time with yourself. Have or develop a system and a pattern in how you resolve or solve problems and use it regularly and recognize it and perfect it.

Many new drugs, not yet on the market, that are using old molecules are close to being released for symptomatic improvement. New L-Dopa formulations(intra nasal, sublingual, oral, and subcutaneous) , and subcutaneous dopamine's are being developed. New drugs are in trials for neuropsychiatric symptoms, for cognitive loss, and dyskinesias. There are many new drugs being investigated for the prevention or delay of progression of IPD (AlDakheel, Kalla).

Other new drugs, not yet released drugs, are being studied. A hypertensive drug, isradipine is still being used in trials, and inosine, an antioxidant is being tested. Inosine is a urate anti oxidant which increases the urate levels and since having high uric acid levels may be related to a reduced chance of having IPD, inosine is and has been in clinical trials. Several diabetic drugs such exenatide are being looked at in some other trials, under the concept that better glucose control may reduce the incidence or progression of IPD or that insulin plays a role. Intra nasal GSH, and glutathione intra nasally is being studied. GM1 ganglioside is being given since it is reduced in the SN of IPD patients. Many ways to enhance immunity are being considered. Stromal cells are

being considered to be given intra arterially or IV. There is no evidence that sub cutaneous, IV, IM stem cells are of any benifit. Treatments surrounding the genetic mutations of LRRK2, GBA, and ATP13A2 are being considered. Pioglitizone, a peroxisome proliferator activated receptor gamma agonist, is being studied and is considered to be reducer of pro inflammatory cytokines. Insulin is thought to play some role in the protein involved in IPD and DAT. Coffee drinking may reduce the incidence of IPD by its caffeine content. Medications that may give an effect on caffeine receptor sites or pathways are being considered as possible treatments. Nicotine or similar molecules have been for years been studied and considered as possible treatment without any clinical benefit as of yet. Monoclonal antibodies, as in DAT trials, are being considered for trials as are several anti cancer drugs. The one drug being used in trials at Georgetown U. is Nilotinib, also known as Tasigna, which is a tyrosine Kinase inhibitor anti neoplastic agent used in leukemia, but it should not be used off label for IPD. It is on the market and currently used in cancer treatment. It will be some time before these drugs will be through the phase II and phase III trials. "Omics" or the study of genomics and proteomics and cellular metabolics, are of great interest not only for new treatments but for finding a marker or markers for the diagnosis of IPD. The difficulty obviously is that Parkinson's disease is a very heterogeneous group of diseases with probably different genetic causes, environmental causes, and variable proteomic involments. One of the newest areas is Inflammation. Involvement is known to occur but what is needed is the understanding of pathology of neurodegenerative diseases especially IPD and its inflammatory influences that occur in IPD and other many diseases. Inflammation is now thought to be major issue, especially in the proteomic and genetic theory. It is thought that the inflammatory process influences the aggregation of the alpha synuclein in some way and or has an influence in the way the protein is released from one cell and or the pathway that it moves to another cell. Inflammation may have an influence on the Proteasomal and liposomal systems. In neurodegenerative diseases like IPD, DAT, LBD, ALS and MS, inflammation is seen with these diseases in humans and in animal models and the inflammatory process has some markers of various types, (blood, CSF and scans) and they document this inflammation. Hence, what may be needed at least in part is to suppress the inflammation which is thought to be one or one of many mechanisms that allow the aggregation and disruption of the cell and gives proinflammatory agents and cytokines, and is in involved in multiple areas. There are and have many trials in neurodegenerative disease, and stroke; however no anti-inflammatory agent has been shown to help in IPD, DAT, LBD, or even in stroke.

The most important concept of Pathophysiology of PD today and the area of greatest interest for therapy is the prion theory. In the prion theory, the alpha synuclein acts as a toxic substance in its oligomer's formation, and has the capacity to act as a template and induce other non effected alpha synuclein to become aggregated and hence more oligomers and form Lewy Bodies and Lewy neurites. This misfolding to oligomers causes neuronal dysfunction in some uncertain manner but probably disrupts synaptic function, alters the membrane by possibly making them more permeable and may trigger an inflammatory response and or effect calcium homeostasis and or mitochondrial activity by effecting Complex I. We know that alpha synuclein spreads according to the Braak classification, as studied by autopsies, through the brain and the other areas of the central and peripheral nervous system in a temporal and geographic manner. It is thought that the prion spreads from on cell to another. In transgenic mice, the prion spreads from cell to cell and has been shown, as a transmission of alpha synuclein, and can be transferred by tissue, between animals as in prion disorders. Now Lewy Body extracts from PD patients and MSA patients can induce Lewy Bodies with in nigrostriatal dopamine system with degeneration and spread to other regions in both mice and primates, but obviously not been shown to spread from one human to another. Now with all this data and information there is active research going on that will use medications to stop the aggregation in some manner or stop its transmission. An obvious treatment considered now (like has been tried in DAT, so far unsuccessfully in trials) is using monoclonal antibodies for the therapy. One trial in normal humans, getting one infusion of PRX002 and followed for 12 weeks has been done safely. More research is being done and new information is pending.

Chronic neuroinflammation has been known and is considered a characteristic of IPD. Microglia or glial cell activation and increased pro-inflammatory cytokines are thought to worsen the signs and symptoms of PD. There is a chronic state with dopaminergic neuron degeneration in the SN as described by Wang. Cx43 up regulation has been determine in striatum of rodent models. The accumulation of aggregated alpha synuclein in intra and in the extra cellular space is thought to be responsible for the transmission and spread of the toxic

oligomers. Inflammation is now considered a major factor in the process of developing neurodegeneration. Inflammation is a response that occurs in CNS injury, stroke, infection or biological stress. It has been shown that extracellular alpha synuclein neurotoxicity is mediated by the P2X7receptors leading to Panx 1 responsible, it is thought for ATP release that may lead to neurotoxicity (Wilkaniec). All of this is of interest because many are searching for an effective treatment for neurodegeneration in many of the neurological diseases. There is inflammation that occurs at the border of a stroke or area of CNS trauma. Microglia activation has a definite pattern and now can be determined on scans. Neuro-glial antigen 2, a proteoglyia expression is found in infarcts as is some cytokines. NG2 is related to secondary neurodegeneration. Microglia also in seen around infracts and ischemia. Virus infection in and around neurons activates neuroinflammation and NG 2. Inflammation brings about neuronal-glia interaction and brings about synapse loss and abnormal neuronal connectivity. There is Bystander -degeneration of neurons and oligodendrocytes and this occurs after injury and may set up a process for progressive changes on a chronic basis.

Today patients, their families and caregivers, and doctors and health care providers are being presented with many issues and problem. What helps all of us to move through this journey in the best possible way for all? One way to approach this is to consider what principles, or values or messages have been given to us through the ages by great writers and books. So what ideas through the ages speak to us today? Which of these thoughts or concepts help us today and have been of value to others for centuries? How do they relate to patient care today? So here seems to be a consensus. For providers, patients, families and care givers, Wisdom (knowledge, education, understanding and information) is of major importance. Justice, Moderation, Courage, Humility, Honor, Responsibility, Honesty, Gratitude, Appreciation, Civility, Decency, and having a conscience (a state or feeling of doing what is right or being driven by a moral code) are all areas that have a value for humans over the many centuries and to us. Each person puts all these values together for themselves and in there daily lives. Many others, such as Virgil, who relates in the Aeneid, that duty is of major importance. But this obviously must be kept with all other values in mind, since O'Brien's behavior toward Winston in 1984 was done because behavior was driven by duty, (someone else determining by control what should be done). Aristotle would relate that understanding is knowing and understanding with Ethos, Pathos, Logos (foundation of logic, data and information), is understanding human behavior.