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Overview of Wellbeing

For over 44 years I have done clinical research, clinical trials and seen thousands of patients, focusing on the neurodegenerative disorders such as Parkinson's Disease, Alzheimer's and Multiple Sclerosis, all possibly manifesting impairment of balance, movements and cognition. A person's genetics, life style, age and chance, will be a great influence on ones Quality of Life and health status as they age and risk significant medical illnesses that most of us will acquire. A key to a better aging life is to avoid accumulating medical deficits such as obesity, nicotine addiction, alcoholism, diabetes, hypertension, stroke and heart disease. The more fragile ones health is mentally and physically, the more likely a person will experience anxiety, depression, apathy, fatigue and reduced activities of daily living. Learn to avoid accumulating mental and physical disadvantages that will deteriorate health care status and increase your family's health care burden. Avoid or reduce health deficits that compromise you and your family as you journey through life. Learn to change a detrimental life style early in life by being an advocate for your future well being.

DEFINITION OF TERMS ANXIETY, APATHY, FATIGUE, FRAILTY AND FEAR OF FALLING

Anxiety is defined as a distress or uneasiness of mind (psychological state) caused by fear, danger, perceived pending misfortune or where outcome of an event is uncertain. It is a state of apprehension and psychic tension.

Apathy is defined as a decrease in goal-directed behavior, withdrawal, loss of motivation, interest, feelings, perception and emotions. There is neglect of grooming, eating and cleaning. The person does not appear to be concerned about this loss. Apathy is often overlapped with anxiety, depression, dementia and fatigue. It said to occur in 50% of Parkinson's disease patients.

Fatigue is usually a constant; however, it can be an intermittent state of weariness, decreased energy, reduced mental capacity, which affects physical and emotional well-being. It is related to:

1. Habits, lifestyle, routines, use of substances such as alcohol, cigarettes, caffeine and reduced activity.
2. Medical problems are associated with fatigue often having some chronicity.
3. Psychological associated symptoms are anxiety, depression, dementia, stress and apathy.

FATIGUE

In Parkinson's disease, fatigue is significantly associated with reduction in quality of life and increased distress in one's life. The frequency of fatigue in Parkinson's disease is 40% before motor signs and 80% after the diagnosis. Fatigue, in many situations, is associated with reduced mobility, emotional well-being, physical function, social interaction and vitality. Depression is probably the strongest risk factor for quality of life in patients with Parkinson's disease. Fatigue is a concept based on the patient's own perceived state of energy or lack of energy. Fatigue is a constant state of weariness that the patient experiences. The patients have reduced energy, mental capacity is reduced and it affects the physical and emotional aspects of the patient's well-being. Fatigue differs from sleepiness, but often fatigue is a desire to sleep and there is a

reduction in motivation. A loss of conscientiousness and inattentiveness is certainly present. Fatigue is often closely related to habits and the person's lifestyle and routine. Routines such as excessive alcohol, excessive caffeine use, smoking, reduced activity, reduced sleep and excessive medication are often related to fatigue. Medical disorders associated with fatigue are many including, but not exclusive, renal, hypertension, heart disease, stroke, diabetes, thyroid disease, obesity, psychological diseases, sleep disorders and obstructive sleep apnea. Fatigue is very closely associated with psychological problems such as anxiety, apathy, grief, depression and stress. Studies have shown that fatigue is associated with more advanced disease of any kind and more with advanced aging. Exercise is probably of benefit in treating fatigue.

Frailty is accumulated deficits and is significantly related to age. It is a nonspecific state of increased risk. Often multisystem diseases are present with gradual increase of these diseases with time and age. Physical and emotional deficits are the key factors. Frailty brings about reduced quality of life, activities of daily living, increased hospitalization and increased costs, and increased office visits. It is related to attention, concentration, function, mobility and balance.

FRAILTY

Frailty and accumulated deficits (lack of or defect) and health status compromise in patients are very interrelated. Frailty is a nonspecific state of increased risk. Frailty is associated with multisystem disease, is somewhat age related and there may not be specific existing known diseases. Specific factors in frailty are difficult to determine, but they are often related to attention, concentration, function, mobility, balance, cognition, depression, apathy and continence. What role these play in daily activities results in the degree of frailty. It is important to avoid accumulation of deficits, especially multi-organ health deficits (i.e.-diabetes, hypertension, stroke or heart disease, lung, renal, liver, neurodegenerative disease or orthopedic compromise). Accumulation is a dynamic process and usually is a greater burden with aging. Some studies show, however, that age alone can have little or minimal impact on deficits.

Appropriate lifestyle to reduce accumulated disease or deficits is paramount. The rule generally is the more diseases you have**,** the more frailty you have, both emotionally and physically and the greater the chance is that you will have more medical problems in the future , hence accumulation of more deficits. Patients with frailty have more signs and symptoms, disabilities, diseases and laboratory abnormalities that indicate diabetes, vascular disease, renal failure, liver diseases. Increased frailty is a very significant indicator that the patient will have greater doctor visits, hospitalizations, and/or institutionalization and earlier death. Frailty is a very considerable cost burden and stress to the caregivers and the family. Women accumulate more deficits than men as they grow older, yet men have a higher mortality rate.

It is important to have awareness in early age of a life style that will reduce disease development and hence reduce accumulation of deficits and disease as you grow older. Encouragement and psychological counseling sometimes are very beneficial along with exercise, a positive environment and mental stimulation.

Fear of falling is a perceived state. Duration and severity depend on a possible related injury and prior history of anxiety. It is usually transient. Its severity is related to the injury that has been the event that brought about the fear of falling. Psychological trauma (fear of falling) is self-imposed. The decline or severity of the state is outside the realm of injury or disabilities. It is associated with reduced healthcare status, quality of life and if unchecked it is related to functional decline. It is related to anxiety, depression, and dementia and there is often a discrepancy between the physical ability and functioning.

FEAR OF FALLING

Fear of falling is a psychological trauma (fear of falling) and is a self-imported decline outside the realms of the actual disability or injury. After falling, the majority of elderly people will have a short period of time that

involves anxiety and is related to their fear of falling. 15% of the falls are associated with fractures or injuries and the patient has awareness that falling can have significant consequences. The duration and severity after the fall is often related to accumulated deficits, which include the patient's prior life journey. This includes medical and neurodegenerative diseases, prior fractures and emotional status that is present at the time of falling. Depression, anxiety, physical ability, and apathy are all related to the degree of fear of falling. Fear of falling has a discrepancy between the physical ability and the functioning that is possible and it is frequently seen in elderly people often more with increasing age and this discrepancy is causally related to social, emotional, and environmental factors that exist at that time. About 50% of people who fall (fallers) have fear of falling and many of them (25%) avoid activities for a period of time. Older age is a very common factor in an increasing incidence of fear of falling. There is a definite concern for self-efficacy, meaning the individual's perception of the capabilities they have with a particular domain of activities or their propensity to fall in certain activities. There is a great deal that depends of one's own deficit and this appraisal is modified by memory, balance, rigidity, slowness, and ability to avoid falls or avoid injury. There are a number of scales such as the Falls Efficacy scale. They help to categorize and rate how the patient will be in their fear of falling and how much they will have for dependency on their family or an agency. An older patient who is in their 80s to 90s often have accumulated frailty and accumulated deficit. Parkinson's, DAT, MS, FTD, chronic illness, depression, anxiety, memory loss all reduce the patient's ability to prevent or avoid falls and injuries.

Treatment is based upon the status of the patient with regard to above-mentioned associated signs and symptoms. Often treatment with behavior modification, physical therapy, reassurance and occupational therapy will help fear of falling. These will give the patient significant confidence in avoiding falls and improvement in their fear of falling syndrome.

MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) is a clinical state with cognitive impairment in the memory domain but has no evidence of dementia. The criteria for the clinical diagnosis is that of a division in the two main forms; 1) is the amnestic form of MCI and 2) is non-amnestic MCI. The amnestic form is thought to have a more rapid advance to developing Alzheimer's disease (AD). MCI already has a few established guidelines and clinical formats to the diagnosis. First, there is a patient complaint of memory loss supported by an informant or caregiver. There is objective cognitive loss (memory impairment) with difficulty with learning and delayed recall in relationship to the patient's age group and educational group. The other cognitive domains are not significantly impaired such as language, executive function, visual-spatial skills and problem-solving. Patients with mild cognitive impairment are having normal functioning activity and they are independent in their home and they have normal activities of daily living (ADL). Their ADL are considered normal by surrounding groups. The determinate is the Mini-Mental State exam and sometimes the MOCA is used and possibly the neuropsychological testing. Amnestic MCI is only memory impairment and this is the group that is most likely to progress to AD. Amnestic cognitive impairment with multiple domains involved usually have dysfunction in attention/executive functions, language, and visual-spatial skills. Non-amnestic MCI single domain is also a sub-group as is non-amnestic MCI multiple domains. The workup for patients with MCI is to obtain laboratory data that will help rule out any other type of secondary memory loss, and the patient should have an MRI. Neuro psychological testing may be an advantage. Biomarkers in CSF values are of uncertain significance but possibly low Abeta amyloid and elevated phosphorylated tau may give some predictive ability, but most physicians do not get these tests. The APOE-4 may be a genetic predisposition. The pathology is intermediate which is in AD patients senile plaques and neurofibrillary tangles, and also many patients will have vascular pathological features. Seventy-five percent of patients with MCI progressed to AD, 25% progressed to other dementias. It is considered that the conversion rate from amnestic MCI to AD is 15% per year for the first 5 years. There is one study thought to be a higher incidence of traumatic brain

injury in patients who convert from MCI to AD. At the present time, there is little evidence for therapeutic benefit from the ACEI medication or other medications.

ALZHEIMER DISEASE (AD)

Alzheimer's is the most common dementia and it is a slowly progressive disorder with memory loss, reduced cognition, associated with behavioral changes and other neuropsychiatric disorders. There are significant features pathologically of neuritic plaques (beta amyloid) and neurofibrillary tangles (tau). Age is the greatest risk factor. The incidence doubles about every 5 years after 65, and at 65 the incidence is about 3-4%. Females have the disease more than males. The signs and symptoms are that of a progressive cognitive decline with significant memory impairment and reduced ability to learn new information. There is a loss of ability to recall past information and there is one or more of the following:

1. Aphasia (language disturbance)
2. Apraxia (inability to carry out and learn motor acts)
3. Agnosia (inability to recognize objects)
4. Disturbance of executive functions which is a loss of planning, organizing, sequencing and abstract thinking.

There are significant neuropsychiatric symptoms that are often seen and they are depression, delusions, paranoia, hallucinations (especially Lewy body disease (LBD)), psychosis, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, and often a spectrum of a Kluver-Bucy clinical picture.

There is often comorbidity in patients with AD and this most commonly is vascular and pathologically is often seen in conjunction with pathological findings of the neuritic plaques (senile plaques) and neurofibrillary tangles.

The workup is to get laboratory data that rules out any other cause of common dementias, and I will not elaborate on that at present, but obviously that includes thyroid, B12 deficiency, renal, liver and other comorbidities. Neuropsychological testing can be done but often is not needed. Neuroimaging, especially with MRIs, helps exclude other diseases but often finds white matter disease or leukoaraiosis in a significant amount. A new test called the PET scanner or the Pittsburgh compound (PiB) scan can show beta amyloid in the PET scanner and often is very helpful in the diagnosis but can have some false negatives and some false positives, somewhere in the range of 90% sensitivity and specificity. There is reduced glucose regional metabolism documented by the FDG-PET scanner and this is usually located in the posterior parietal area. On the MRI there is often atrophy in the hippocampus or the temporal lobe volume is reduced. Genetic chromosome 1, 14, and 21 are associated with AD and 90% of the APOE-4 patients had abnormal pathology on autopsy and reflect that it is shown that APOE-4 is a risk factor for AD. If a spinal tap is done, CSF shows reduced levels of beta amyloid 1-42 and this CSF tau (tau phosphorylated) is present and the sensitivity and specificity is around 85%.

The most current and scientifically support concept for the etiology is it is thought that there is an abnormal processing or deposition of the beta amyloid called the amyloid cascade. Abeta 1-42 fragments of APP (amyloid precursor protein) are generated due to probably abnormal cleavage of the APP which is usually cleaved by the alpha secretase (a protease). But in AD this APP is abnormally cleared by beta and gamma secretases. Hence, AB 1-42 is formed and is positive in the brain and is insoluble in its aggregated form. This is the beta amyloid cascade event which is thought to then be associated with inflammatory changes and cell death.. There may well be other processes but this appears to be the primary one or at least part of a double

hit. There is also the neurofibrillary tangle or tau and the exact role is uncertain but seems to play a role in the pathological process. There are certain studies being done on the way APP is broken down and on the action of alpha secretase, beta secretase and gamma secretase and how this cascade takes place.

Treatment at the present time is only symptomatic. The acetylcholinesterase inhibitors (ACEI) which are 3 are used as is a glutamate antagonist. The ACEI therapy is based upon clinical trials which show that donepezil, rivistigamine and galactamine have all been of benefit clinically. The basis of this treatment is that there is a known cholinergic deficit in brains of AD patients. It has also been shown that Axona, a mid-chain triglyceride, is of some benefit. Selegiline and vitamin E have been used and this may benefit clinically and acts as an active antioxidant. A recent study shows that vitamin E may be of benefit.

For depression SSRI's (selective serotonin reuptake inhibitors) or tricyclics have been used for depression. Both work but the tricyclics have some possible adverse side effects that are anticholinergic. Also selective norepinephrine reuptake inhibitors or dual inhibitors have been used but all of these agents have limited trials.

For psychosis, quetiapine (Seroquel) is an atypical neuroleptic which probably has fewer side effects than the neuroleptics, but studies have been variable in its results. Risperidone has higher extrapyramidal adverse effects but also is of benefit and olanzapine has been used. Rarely haloperidol has been used but that has significant side effects including the risk of tardive dyskinesia. For apathy, the ACEI drugs may be used but also dopamine agonists, SSRI's, SNRI's have been used. For agitation, trazodone an anti-psychotic agent may be used.

Various levels of certainty to the diagnosis are present especially where the disease is seen early. It is best if the clinical diagnosis fits clinically with the above features and that there is an abnormal MRI (no structural lesion but hippocampal atrophy, a positive amyloid PET scanner, an abnormal glucose PET scanner and abnormal CSF. However most workups do not include all of these, and most include getting an MRI to rule out other diseases along with other extensive lab work. AD is a spectrum of clinical features, everybody has their own individual disease and they have it with and without varying degrees of comorbidity knowing that the most prominent comorbidity is the vascular impact.

Anti-inflammatory medication had been studied to treat AD but so far there has been no evidence of benefit, but there is still are some pending trials, especially COX 2 inhibitors and NSAIDS. Estrogens failed and had a higher incidence of thrombophlebitis and did not seem to be protective.

There have been many trials and considerations for treating AD using the concept of the amyloid cascade. Beta amyloid is in the senile plaque and it is a major component and it is thought to be toxic to the neurons. Beta amyloid is processed by proteinases alpha, beta, and gamma secratases, and they generate beta amyloid. Hence, it has been considered the therapeutic possibility to inhibit the secratases; however, so far numbers of trials have been negative. Immunizations have been used against beta amyloid. In knockout mice, immunization was done and these mice had less plaque formation and later there was regression of plaque formation. Human trials of Abeta 1-42 immunizations had adverse side effects, one of which was a 5% incidence of meningoencephalitis. However, if the human patient developed antibody levels there may have been some possible benefit and possible reduced loss of volume on the MRI. Amyloid anti-aggregation agents, such as tramiprosate, have had no value. The antihistamine Dimedone was studied in Russia and it was thought there was a possibility that it had some benefits. Other test trials are pending. Monoclonal antibodies were thought to have possible effectiveness against the beta amyloid, but so far trials have been of no benefit. In current trials, agents against tau oligomers are being studied. The IVIG trials were done and probably had no clinical benefit in the total assessment, however this would be a very expensive treatment format.

WELLBEING IN PARKINSON'S DISEASE (IPD)

The Wellbeing in Idiopathic Parkinson's Disease (IPD) is determined by Quality of Life (QOL) and Activities of Daily Living (ADL). Certain scales or measurements determine QOL and ADL. These are measures (UPDRS and PDQ39) of motor control and non-motor symptoms as well as cognition. The neuropsychiatric (NP) signs and symptoms are somewhat included, but measurements are difficult; however, their symptoms can be very detrimental to a patient's QOL and ADL. A patient today with IPD can live 20 years or more after the diagnosis of IPD if they avoid comorbidities such as cancer, diabetes, obesity, hypertension, vascular disease (stroke and heart disease), and renal and pulmonary disease. Some of these are determined by genetic predisposition, but many are related to habits and lifestyle. Trauma (like falls with head injury and fractures) reduce QOL, ADL, and survival. Hence, trauma such as head injury and falls must be avoided and if possible, prevented. Much of this comorbidity (additional disease) accumulates deficits and is associated with accumulated motor and non-motor deficits which affect QOL and ADL. Accumulated deficits may be genetically determined in part, but even these are influenced by our lifestyle. To avoid or delay much of these deficits, a healthy lifestyle should be established early in life since most of these diseases or comorbidities have early pathophysiological changes 10 or more years before clinically obvious. This is certainly the case in neurodegenerative diseases such as IPD and Alzheimer's (DAT). Brain changes occur years before the symptoms appear.

At the recent American Academy of Neurology (AAN) in April, multiple studies documented in animal models and in patients that exercise not only gives better scores on Parkinson's measurement (UPDRS) but also on QOL and ADL measurements. Exercise results in better motor strength, balance, gait, conditioning and endurance, which always benefits the patients. This exercise must be done almost daily and to near maximum heart rate (60 to 80% Max HR). Exercise and a healthy diet benefits most comorbidities.

There is evidence that neuropsychiatric signs and symptoms affect QOL. These NP symptoms are depression, apathy, anxiety, fatigue, frailty, and fear of falling. These symptoms can have a profound effect on QOL and ADL. Depression occurs in 30% to 50% of IPD pre-diagnosis and probably higher after the diagnosis. Mild cognitive impairment (MCI) occurs in 10% to 20% of patient at the time of diagnosis. MCI is loss of memory for recent events without signs of DAT. In IPD, cognitive impairment at 8 to 10 years after the diagnosis occurs in 60% to 80% of patients. It appears to be more prominent in patients who are older, and had the disease longer, have neuropsychiatric symptoms and are at higher dosages of medication. Pathologically, cognitive impairment in IPD is a mixture of Lewy body pathology (DLB), DAT, and vascular changes.

In order to recognize NP symptoms, we have to understand how they are defined. Anxiety is defined as a distress or uneasiness of mind (psychological state) and causes of anxiety are fear, danger, perceived pending misfortune or where the outcome of an event is uncertain. It is a state of apprehension and psychic tension. Apathy is defined as a decreased in goal-directed behavior, loss of motivation and interest, loss of feelings and emotion, and often overlapped with anxiety, depression, dementia, and fatigue. Anxiety occurs in about 50% of Parkinson's disease patients. Fatigue is usually a constant state and occurs in 70% to 80% of patients with IPD. However, it can be an intermittent state of weariness, decreased energy and reduced mental capacity; all of which affects physical and emotional well being. Fatigue is related to many aspects of the person's life. Habits, lifestyle, routines, use of substances such alcohol, cigarettes, caffeine, and reduced activity are often related to fatigue. Chronic medical problems are often associated with fatigue. Psychologically associated signs and symptoms are anxiety, depression, dementia, stress, and apathy.

Frailty is accumulated health deficits, which affects healthcare status and is often significantly related to age. It is a non-specific state of an awareness of increased risk. Often multisystem diseases are present with

gradual increase of these diseases' burdened with time and age. Physical and emotional deficits are key factors to frailty. Frailty brings about reduced QOL, ADL, increased hospitalization, increased healthcare cost, and increased office visits. Frailty is associated with reduced attention, concentration, function, mobility, and balance.

Fear of falling is a perceived state. Duration and severity depend on related injury and prior history of anxiety. It is usually transient and its severity is related to the injury that has preceded the event and brought about the fear of falling. Psychological trauma (fear of falling) is self imposed. The decline or severity of the state is usually outside the realm of injury and disability. It is associated with reduced healthcare status, QOL, and if unchecked, it is related to significant functional decline. There is a discrepancy between physical ability and functioning.

Exercise, healthy diet, non-smoking, and weight loss all reduce the chances of acquiring cumulated comorbidity and hence acquiring deficits and reduction in healthcare status.

These entities or deficits that affect QOL and ADL need to be recognized and discussed. The foundation for therapy is optimized, pharmacological management and if needed, psychological counseling. Exercise, conditioning, reassurance, adequate sleep, support, possibly counseling, and medication will help reduce the impact of the above symptoms on the patient and on the caregiver's QOL.

CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

Chronic traumatic encephalopathy is a clinical entity which is secondary to repetitive trauma of various degrees of severity. Most of the history of trauma is probably multiple and includes grade III concussions which involves loss of consciousness. It certainly can involve more severe trauma. There is an uncertainty as to the number of traumas it takes and the severity of the traumas to develop CTE. The patients with CTE have a progressive, gradually worsening clinical condition which is associated with multiple types of signs and symptoms. The most important is behavioral changes. The patient can develop behavior and personality changes that are gradually progressing. These behavior changes can be associated with depression, irritability, impulsiveness, apathy, fatigue, anxiety, and even suicide. The severity of the depression has a wide spectrum that may involve signs and symptoms of depression which can be crying spells, weight loss, reduced appetite, sleep disturbances, withdrawal, and suicidal ideation. Parkinsonism is often seen in patients with CTE. Patients will develop a symmetrical rigidity, bradykinesia or akinesia and often will develop masked fascies along with stoop posture and flexion of the extremities and shuffling with walking. Balance difficulty with posture instability can also be seen. Dementia is the symptom that may occur later in the disease and is usually preceded by behavioral changes. There is memory loss, especially recent memory loss. Attention span is reduced. Appropriate social awareness and the usual conscientious behavior is often reduced. There is significant executive dysfunction with visual and social changes. There is loss of processing speed and judgment may become inappropriate. Reasoning is affected and problem solving is significantly changed. Generally, in CTE, the symptoms develop gradually and progress over years and can occur years to decades after the trauma. The PET scan will often be abnormal, especially in the temporal areas, but sometimes also in the frontal area. The pathology is that of Tau pathology without significant beta-amyloid changes such as senile plaques. The Tau pathology is usually seen in the tips of the temporal lobe in the hippocampus and also in the frontal superficial cortical area. CTE is obviously a diagnosis by exclusion and these patients must be worked up to rule out a metabolic, endocrine or a structural abnormality. The spinal fluid will usually be normal but if levels of amyloid and Tau are obtained, the amyloid is usually in normal range and the Tau is elevated. Most importantly, structural lesions such as stroke, subduals and tumors need to be ruled out.

REM Behavior Disorder

Rapid eye movement sleep behavior disorder (RBD) is a sleep disorder, which is characterized by loss of a normal muscle paralysis (atonia) during a period of time when the patient is asleep when they are having rapid eye movements (REM) and the patient with RBD develops prominent motor activity during the time of dreaming when they are acting out their dreams. There are several key features clinically to RBD. First is dreams that have some type of abnormal content in which the patient usually is fighting or protecting himself against some attacker, which can be almost anything, and these dreams are interpreted as severe nightmares and are undesirable, unpleasant and oftentimes can be remembered upon awakening. The second part of RBD is the significant abnormal vocalizations, which could be from screaming, shouting or bursting out in laughter. The third and fourth feature of RBD is the significant abnormal movement, which oftentimes are anticipated by brief repetitive jerking or movement, then are oftentimes followed but not always by significant forceful purposeful activity that seems to be done in a manner to protect themselves. This abnormal movement activity can be that of trashing out, flailing, jumping, running or throwing things or grabbing the bed partner and inflicting injury. The main clinical complications of RBD are injuries that can occur to the bed partner or to the patient such as fractures of the arms, legs, skull subdural hematoma or especially hip fractures or pelvic fractures.

The diagnosis is made by a careful history from the bed partner and from the patient. The bed partner obviously is the best historian, but the patient may well remember the tearfulness or the trauma of the dream. The patient will oftentimes remember quite vividly some of the features of the dreams and their exact character.

Characteristically, RBD occurs in the latter part of the sleep period, usually from about 2 a.m. to 6 or 7 a.m. This is quite characteristic for most patients. The frequency can be very infrequent. If the RBD occurred 10 to 15 years before, the episodes may have been very infrequent, but oftentimes it becomes more frequent and can occur as often as 15 to 20 nights a month. The range in severity is significant in that they may be very mild or may be quite severe.

It is important to make the diagnosis of RBD and the history usually is insignificant enough to make the diagnosis, but sometimes the caregiver or family can videotape the patient during the night or, if needed, a polysomnography monitoring can be done overnight. The problem with ordering the test is that it may not occur that night and it is quite expensive. Differential diagnosis is important in that there are forms of nocturnal epilepsy that can mimic RBD and also obstructive sleep apnea at times can mimic RBD.

The underlying pathophysiology is uncertain but it appears to be involved with the brainstem and that apparently has some abnormalities along with local motor generators that project to the motor neurons and the brainstem. The exact pathology is uncertain. There have been many animal model studies; however, they have only resulted in limited information.

Therapy and management are very essential especially education of the patient and of the bed partner in the family. The key is to minimize injury. This has to be done on the basis to eliminate objects around the patient that would be injurious and taking other precautions that may help reduce injury. Medication is almost always needed in patients with RBD. My algorithm for the treatment is to consider melatonin in some cases and I usually start out at 3 mg per night and gradually increase it about every week up to a maximum of 12 mg a night. This can be purchased over-the-counter. Most commonly, however, the patient needs clonazepam (Klonopin) and that can be used and is oftentimes quite successful. I start at 0.25 mg at night and gradually increase it about once every week up to about 1 mg if needed. Clonazepam has to be used very cautiously in

patients who have cognitive impairment or have obstructive sleep apnea (OSA). Combination therapy using melatonin or Klonopin as an add-on drug is certainly possible. If there is failure with those drugs, then my algorithm for treatment goes next to pramipexole, levodopa, donepezil, carbamazepine, Seroquel and last Clozaril. Some people have also used drugs such as donepezil and Namenda.

Diagnosis early is important and treatment is essential to avoid injury. The 30% to 40% of Parkinson's patients have RBD and oftentimes anticipate Parkinson's disease as it may in Lewy body disease, multisystem atrophy or in some other neurodegenerative diseases. Studies show that if the patient has REM behavior disorder as a single diagnosis, 50% to 60% of the patients will develop either Parkinson's disease or Lewy body disease or another neurodegenerative disease.

Dee Silver M.D. 03/02/2015