**Subject:**[StanfordPDInfo] Recognizing and Treating Non-Motor Symptoms - good article

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The American Parkinson Disease Association funds 50+ half-time information and referral centers around the US. (The center for Northern California is based at Stanford.) Some of the center's have very professional newsletters. The latest issue of the "Minnesota Messenger" showed up in my mailbox this week. There's a terrific article in it on non-motor symptoms of PD. I've copied the article below, and given you a link to it.

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**RECOGNIZING AND TREATING NON-MOTOR SYMPTOMS IN PARKINSON’S DISEASE**by Okeanis Vaou, MD, Neurologist, Movement Disorder and Sleep Specialist, Noran Neurological Clinic PA, Minneapolis, MN

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While motor symptoms are the most common in Parkinson’s disease and are used for diagnosis, the non-motor symptoms dominate the Parkinson’s patient life and may also be missed in the doctor’s visit. These include fatigue, depression, sleep disturbances, constipation, bladder and other autonomic disturbances (sexual, gastrointestinal, cardiovascular) and sensory complaints, such as pain. Other common complaints include bradyphrenia, confusion, dementia, lack of motivation and apathy, behavioral changes in mood and hallucinations. Based on the Braak theory, olfactory and autonomic disorders predate motor PD symptoms by 20 years (Hawkes et al 2010).

A recent study of more than 1,072 PD patients revealed more than 98.6% had non- motor symptoms which were bothersome. In addition, medications used to treat the motor symptoms, often times worsen the non-motor symptoms, such as orthostatic hypotension.

**Pain**
Many patients experience shoulder, leg or back pain prior to the onset of motor symptoms of PD. These patients are usually evaluated for pain by other specialists such as orthopedics, and diagnosed with arthritis or frozen shoulder. This pain is a constant dull pain, most of the time related to PD, and is usually relieved with PD medication. Another cause of pain in PD patients is leg cramps, which appear during off states or during walking, and improve with dopaminergic treatment.
 **Hyposmia**
Hyposmia, reduced ability to smell and detect odors, has been found to be a symptom preceding the onset of motor symptoms of PD by an average of four years (Ross, et al 2008). Decreased sensation of smell is not typically a common complaint of patients with PD, but in one study 45% of PD patients were anosmic, 57.1% were hyposmic and only 3.3% were normosmic (Haehner at all, 2009). Hyposmia is now being studied to be used for early PD diagnosis.

***Autonomic Nervous System***

**Bladder**
Urinary urgency is one of the most common symptoms in PD. Detrusor hypereflexia and uninhibited bladder contractions causes urinary frequency and nocturia, which troubles patients with PD, waking them up at night and causing fragmented sleep. This usually is prevalent in the elderly male group. Treatment of urinary urgency and frequency with a peripheral antimuscarinic agent, such as oxybutinin, is helpful. A tricyclic antidepressant may also be used to improve sleep, as well as urinary urgency.

**Orthostatic Hypotension**
Orthostatic hypotension may present as a feeling of lightheadedness, pre-syncope or syncope, may worsen the cognitive state, and cause symptoms of fatigue, weakness or blurry vision. This happens because PD affects the autonomic nervous system and in particular, both the parasympathetic ganglion neurons and sympathetic cardiac plexi (Kupsky et al. 1987). This affects the vasoconstriction and blood pressure control. In addition, levodopa, dopamine agonists, and selegiline decrease blood pressure. Patients with PD rarely have orthostatic hypotension as severe as patients with MSA (multiple system atrophy).

Increasing fluid and salt intake, compression stockings, and exercise to calf muscles are some of the conservative measures to increase blood pressure. However, if this is not enough to treat hypotension, Fludrocortisone, Midodrine or Pyridostigmine may be considered.
 **Gastrointestinal**
Due to parasympathetic dysfunction in PD patients, the gastrointestinal (GI) system is also affected. Gastric dysmotility with delayed gastric emptying affects digestion. Symptoms of bloating, reflux and indigestion are some of the resulting symptoms (Edwards et al. 1992). Gastric emptying can also affect levodopa absorption, leading to medication failure or inadequate treatment.

One of the most common complaints among PD patients is **constipation**. This is due to many factors, such as parasympathetic dysfunction, decreased fluid intake and immobility. Usually increasing dietary fiber, vegetable, fruit and fluid intake, as well as exercise can be helpful. Medications commonly used, such as polyethylene glycol powder (Miralax) and other laxatives can adequately treat constipation. In severe cases, apomorphine can help with constipation. Studies have also shown that intrajejunal use of duodopa has helped with constipation and other bowel symptoms (Honig H, Antonini A, Martinez-Martin P, et al. Intrajejunal levodopa infusion in Parkinson’s disease: a pilot multicentre study of effects on non-motor symptoms and quality of life. Mov Disord).

**Sialorrhea**
Increased salivation and drooling is seen in 31% of PD patients. This occurs mostly because of decreased frequency of swallowing, rather than overproduction. Chewing on candy or gum is an easy way to overcome drooling and excessive salivations. If this is not effective, medications such as peripherally acting anticholinergics glycopyrrolate or propantheline can be helpful. In medically refractory cases, neurotoxin injections to the salivary glands can decrease production of saliva.

**Sleep Problems**
Most patients with PD have problems related to their sleep, such as insomnia, interrupted sleep through the night, commonly known as sleep fragmentation, REM behavior disorder, excessive daytime sleepiness, and altered sleep wake cycle. Such sleep problems have a major impact on patients with PD and their caregivers. Most sleep disturbances occur as the disease progresses and are seen in 40-90% of cases (Tandberg et al, A community-based sleep study of sleep disorders in a patients with Parkinson’s Disease, 1998).

**RBD**
REM sleep behavior disorder (RBD) is the loss of normal REM sleep atonia, which manifests as dream reenactment. Typically, patients act out their dreams, and this may result in an injury to them as well as their sleeping partner. The patients may scream, yell, kick or thrash in their sleep, with no recollection the following morning. RBD may precede the onset of PD by 12.7+/- 7 years and may serve as an early marker for PD (CH Schenck, MW Mahowald REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP Sleep, 25 (2002), pp. 120–138). A study following patients with idiopathic RBD found that their risk of developing neurodegenerative disease, including PD in 10 years was 40.6% and in 12 years 52.4% (Postuma et al, 2009). In another study of PD patients, 33% were found to have RBD (Scaglione et al 2005).

Clonazepam or Melatonin is the most effective treatment for RBD. Gabapentin, Levodopa and Pramipexole have been reported to provide some benefit in isolated cases (ML Fantini, J-F Gagnon, D Filipini et al. The effects of paramipexole in REM sleep behavior disorder Neurology, 61 (2003), pp. 1418–1420).

**Excessive Daytime Sleepiness**
In many patients with PD, excessive daytime sleepiness is a common problem. This occurs in 15% of PD patients, and is more common in more severe Parkinson’s disorder associated with dementia. In such cases, EDS was found in 50% of patients (Shpirer at al, 2006). Dopamine agonists may be contributing to EDS and should be decreased or stopped if the patient feels drowsy following a dose of dopamine agonists. In severe cases, PD patients sleep most of the day and are awake during the night, causing great frustration to the caregivers who usually follow a normal sleep-wake pattern. In such cases, it is important that the patient shifts back to a sleep schedule that is similar to that of the caregiver. This can be achieved by keeping the patient awake during the day, either by increased mental as well as physical activity, and if necessary, by stimulants such as modafinil, methylphenidate and amphetamine. Exposure to sunlight during the day, and avoidance of stimulants or caffeinated beverages during the evening can be helpful. For adequate sleep at night, a hypnotic may be added to the daytime stimulant.

**Sleep Fragmentation**
Sleep maintenance is a major problem in the PD population. Sleep is fragmented due to frequent urination as a result of urinary urgency, increased muscle stiffness and trouble turning over in bed as the daytime dopaminergic therapy wears off. Another frequent complaint is interrupted sleep, as a result of REM behavior disorder and periodic limb movements of sleep.

***Disorders Of Behavior***

**Depression**
One of the most common concerns in PD patients is depression, which may precede motor symptoms of PD, or occur as PD progresses. One study showed a 28% prevalence of depression in PD patients (Ravina et al, 2007). In a different study, depression affected 45% of PD patients (Chaudhuri et al, 2006). Depression in patients with PD is a factor of impairment of activities of daily living.

There have been several suggestions for the reasons for depression experienced by patients with PD. A patient with PD faces many challenges due to his motor disabilities, and may have to give up a fraction of his or her independence.This, along with the diagnosis of an incurable, chronic and debilitating disease, increases the risk for depression. On the other hand, the pathology of PD itself may be the cause, affecting, the serotonergic and noradrenergic neurons in the limbic system, typically involved in primary depression (Bejjani et al. 1999).

The recognition of depression in PD patients is very important and treatment can improve activities of daily living. Most commonly, SSRIs, are effective in treating depression. Of the dopamine agonists, pramipexole, used to treat motor symptoms of PD, has shown antidepressant activity similar to fluoxetine, and was better than placebo in 174 patients with PD and depression (MH Corrigan et al, 2000).

**Anxiety**
Anxiety frequently coexists with depression in patients with PD. Patients feel anxious in social or professional settings, and fear that they will not perform adequately, or that their friends and relatives will notice their motor or verbal disabilities. Anxiety also tends to worsen during “off” states. Treatment with dopaminergic therapy is usually effective in treating anxiety.

Depression and anxiety can also occur as the sensory or behavioral “off. Similar to the motor off, this occurs when there is insufficient dopaminergic activity, mostly to the limbic system and therefore responds to dopaminergic therapy aimed at preventing wearing off (IH RIchard et al Anxiety and PD disease, 1996).
 **Lack of Motivation**
Personality disorders may manifest as a lack of motivation and restriction of activities. The patient may find it difficult to multitask or make important decisions at work, and may not be able to continue working. The patients become more passive and dependent on their caregivers. They tend to become less interested in social activities and prefer to stay home. In severe cases, the patient develops apathy and abulia with complete lack of motivation and initiative. Such changes may be related to depression, but most times there is no mood change. Although dopaminergic therapy can be effective, a small study has suggested that stimulants such as mehtylphenidate have proven to be effective (Chatterjee et al, Methylphenidate treats apathy in Parkinson’s disease, 2002).

***Cognitive Problems*
Dementia**
Unfortunately, in the late stages of PD, a large portion of patients develop dementia. PD dementia is characterized by impairment in attention, memory, executive and visuospatial functions. In addition, behavioral symptoms such as changes in affect, hallucinations and apathy are frequent (Emre et al, 2007). Dementia can affect up to 80% of late stage PD patients (D Arsland et al, Prevalence and characteristics of dementia in PD, 2003). According to one
study, patients with akinetic-dominant or mixed tremor/akinetic PD have a higher risk of developing dementia (Aarsland et al, 2003). In a different study, it was found that patients with end stage PD who had dementia, had worse “on” and “off” motor periods and a smaller response to levodopa (Alty et al., 2009). Treating dementia in PD patients can be challenging at times. Before treating dementia in patients with PD, secondary and potentially reversible causes need to be ruled out. Such causes include infection, metabolic abnormalities, subdural hematoma, hypothyroidism and seizures. Medications which are frequently used in PD and can worsen dementia should be decreased or discontinued. These include selegiline, anticholinergic medication, amantadine and dopamine agonists such as pramipexole and ropinirole. Donepezil and Rivastigmine have been shown to provide moderate benefit in dementia. Hallucinations, which frequently coexist with dementia in PD patients, can be treated with quetiapine without exacerbating parkinsonian symptoms. Clozapine is also effective in treating hallucinations, however, weekly checking for neutropenia makes this a less favorable choice.

**Hallucinations**
Visual hallucinations are reported in 16-37% of drug treated Parkinson’s Disease patients, and are the most common hallucinations in PD. Auditory hallucinations are relatively uncommon. Hallucinations are perceptions that are not based on any relevant stimulus. Delusions are false, irrational beliefs that are not based on data. In general, these are distinct phenomena, although both may occur in PD psychosis. They are usually a result of the disease itself, the side effects of medication, and occasional illnesses such as infections or metabolic disorders.

Visual hallucinations often start by a sensation of presence, described as a shadow in the peripheral vision, which quickly disappears once the patient tends to it. More severe hallucinations may take the form of an animal or person with usually retained insight and are generally not bothersome to the patient.

Management of hallucinations most times begins with exclusion of secondary causes such as underlying infection, metabolic derangement, renal, hepatic or endocrine dysfunction, cancer, stroke, etc. Hallucinations in Parkinson’s Disease patients can be treated with antipsychotics, such as Clozapine or Quetiapine, without worsening PD symptoms. Clozapine is not the preferred medication due to the frequent blood monitoring for side effects of agranulocytosis. Quetiapine is the medication most frequently used to treat hallucinations. Due to sedative properties, Quetiapine is commonly given before bedtime and can serve as a sleep aid and improve sleep. If hallucinations persist, discontinuation of Selegiline, Amantadine and anticholinergics should be considered, and dopaminergic agents should be reduced if possible.

The material presented regarding medication is for information only and should not be used for individual treatment purposes, rather for discussion with the patient’s own physician who is knowledgeable about the individual’s history. It does not reflect endorsement.
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