

Background of Article Review

Neuropsychiatric symptoms, or mental disorders associated with nervous system dysfunction, are common features of Parkinson's disease (PD) that affect a majority of patients with PD. Since these symptoms significantly impact patient quality of life and worsen the functional impairment already experienced in PD, researchers are concerned with developing better, more efficient ways of clinically approaching these symptoms.

Accordingly, a team of researchers composed of Dr. Dag Aarsland of Stavanger University Hospital (Norway), Dr. Laura Marsh of Johns Hopkins University School of Medicine (Baltimore, MD) and Dr. Anette Schrag of University College Department of Clinical Neurosciences (England), published an article reviewing the findings of several research studies on neuropsychiatric symptoms in PD. This review, published in the *Movement Disorders Journal* (Vol. 24, Issue 15), discusses the causes, clinical features, diagnosis and management of some of the most common neuropsychiatric symptoms in PD patients, including:

- *Depression, a psychiatric condition characterized by sadness and emotional withdrawal;*
- *Anxiety, a state of apprehension or mental tension;*
- *Apathy, a debilitating lack of interest or motivation;*
- *Fatigue, a state of extreme physical or mental exhaustion;*
- *Psychosis, a severe mental disorder usually causing impaired sense of reality.*

Purpose of the Study

The purpose of this article review is to address the need for more conclusive clinical studies on these neuropsychiatric symptoms, as well as to evaluate existing research findings on the management (both drug-related and non drug-related) of these symptoms.

Anxiety & Depression in PD:**Prevalence and Pattern of Occurrence:**

Depression and anxiety can emerge years before PD motor symptoms develop, falling under the category of non-motor symptoms that potentially foreshadow PD. Of the total number of patients with PD, approximately 30-40% has significant symptoms of depression, while up to 40% is affected by anxiety.

Clinical Features of Anxiety & Depression in PD:

Clinical Features of Anxiety in PD:

Researchers speculate that anxiety may be part of an underlying depressive disorder; however, they have discovered no apparent relationship between anxiety and severity of motor symptoms or *dementia* (severe decline in memory and other thinking skills) in PD. The most common anxiety-related disorders in patients with PD are:

- Panic attacks;
- *Generalized anxiety disorder* (GAD), a condition of frequent, constant worry and anxiety over many different activities and events;
- Specific and social phobias.

Clinical Features of Depression in PD:

The key features of depression in PD are low mood and lack of interest or pleasure. Other common features of depression in PD include:

- Altered appetite or sleep;
- Weight change;
- Loss of *libido*, or sex drive;
- *Psychomotor retardation*, or the general slowing of mental and physical activity;
- Reduced memory;
- Loss of energy.

Feelings of guilt or worthlessness and developing suicidal thoughts are also apparent in some PD patients with depressive symptoms, although these features are rare.

Of note, in patients with advanced PD it can be especially difficult to distinguish the common physical features of depression from the same features that are commonly found in patients with PD [features not attributable to depression] such as:

- Slowness of movement and thinking;

- Loss of appetite and weight;
- Sleep problems.

Diagnosis, Assessment and Classification of Anxiety & Depression in PD:

Accurate diagnosis of anxiety and depression in PD is difficult due to the overlap of Parkinson's symptoms and other non-motor symptoms. For instance, a Parkinson's patient with low energy, sexual dysfunction and *flat affect* (severely reduced emotional expressiveness) could easily be diagnosed as depressed, even though these symptoms stem from their neurological disease rather than a mood disorder. To combat these difficulties, researchers advise that diagnosis of anxiety or depression in PD should only be made using clinical criteria (as identified by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – Text Revision (DSM-IV TR)) rather than just clinical scales administered to patients.

Management of Anxiety & Depression in PD:

Researchers advise taking the following steps to best manage anxiety and depression in PD:

1. The first step is to determine whether the depression and/or anxiety symptoms occur solely during PD off-periods, or phases of increased difficulty moving and reduced response to medication.
⇒ If so, then antiparkinson medication should be adjusted, since persistent neuropsychiatric symptoms often result from under-medication during PD off-periods.
2. Secondly, the severity of symptoms should be determined in order to assess the need for treatment.
⇒ This is because in most cases with mild depression (the majority of cases) non drug-related intervention is the treatment of choice, such as counseling or patient education.

As of yet, the success of drug-based therapies in anxiety is unknown due to the inadequate assessment of anti-anxiety medications in PD. Although selective serotonin reuptake inhibitors (SSRIs) are currently the preferred treatment of PD anxiety disorders, their therapeutic value has not been established.

On the other hand, there are several approaches to the treatment of depression in PD in addition to the aforementioned first and second points:

- *Dopaminergic medication*, treatments used to modify levels of the chemical dopamine;
- *Psychotropic medication*, drugs used to treat anxiety and depression or other psychological disturbance;
- *Electroconvulsive therapy* (ECT), electroshock therapy known to improve depression that is otherwise not helped by medications;

- *Repetitive transcranial magnetic stimulation (rTMS)*, a noninvasive method to excite neurons in the brain using magnets.

It is important to speak to your treatment providers in length about the possible benefits of specific treatments, particularly in the context of what the research literature reports. When it comes to medication therapies for depression in PD, researchers stress that both clinicians and patients consider the potential side effects of these medications (particularly in the elderly), as well as their possible interactions with other drugs. In addition, consideration should be given to the chance of worsening motor functions and increased likelihood of non-motor and dopamine-related PD complications.

Apathy & Fatigue in PD

Apathy and fatigue are two common non-motor disturbances in patients with PD that:

- Largely contribute to disability;
- Play a role in causing diseases that affect certain regions of the brain;
- Are attributed to disrupting the connections in the frontal area of the brain.

In both apathy and fatigue, mood symptoms and loss in *cognitive* abilities (thinking skills) are also frequently present. Both apathy and fatigue can occur as a feature of a medical condition (such as PD) or as independent symptoms (feeling apathetic and/or fatigued without having those symptoms being directly attributed to a medical, such as PD, or psychological condition, such as depression). However, regardless of the severe impact of these symptoms, few studies have addressed apathy or fatigue in PD and better detection and more effective treatments are needed for both.

Prevalence and Pattern of Occurrence:

Prevalence and Pattern of Occurrence of Apathy in PD:

Most studies used clinical rating scales to define the presence of apathy. According to these studies, apathy is present in 17-70% of PD patients. This large difference in the reported presence of apathy is influenced by the following factors:

- The severity of depressive symptoms and cognitive impairment in the patient sample;
- The assessment tools used;
- The person rating (i.e. a clinician, family member, or patient).

Apathy symptoms in the absence of depression occurs in 4-30% of patients (14% on average), whereas the reported prevalence of apathy coexisting alongside depression is 12-47%. Apathy is also a feature of

dementia, delirium, and demoralization and can occur in the absence of cognitive impairment. However, the long-term course of apathy has not yet been studied.

Prevalence and Pattern of Occurrence of Fatigue in PD:

Fatigue is the single most disabling symptom reported by up to a third of patients with PD. It has a reported prevalence of 32-58%, which is also influenced by inconsistent definitions of fatigue and by the type of assessment instrument used. Like anxiety and depression, fatigue is present early in the course of PD and may even precede the arrival of motor features. In PD, fatigue is also frequently associated with:

- Depression;
- Cognitive deficits;
- Daytime sleepiness.

Once present, fatigue can be chronic or intermittent, although its duration generally increases over time. Nevertheless, despite its prevalence and impact, fatigue is still under-recognized clinically.

Clinical Features of Apathy & Fatigue in PD:

Clinical Features of Apathy in PD:

Apathy refers to a set of behavioral, emotional and cognitive features that involve:

- Reduced interest and motivation in goal-oriented behaviors;
- Indifference;
- Flattened affect (severely reduced emotional expressiveness).

Typically, patients show poor motivation with reduced initiative, effort and determination, as well as indifference to their circumstances. This is marked by:

- A lack of spontaneous engagement or early withdrawal in activities;
- A lack of concern for one's own health;
- Absence of curiosity about others or new experiences.

The role of depressive disturbances in patients with apathy is also significant. However, reports are inconsistent as to whether the combination of apathy and depression is more common than either apathy without depression or depression without apathy. In one study, apathy and depressive scores were significantly related in patients with PD, whereas in patients with disorders other than PD, they were less clearly related. Researchers have also found that apathy in patients with PD is often associated with:

- *Bradyphrenia*, slowness of thought;
- *Cognitive impairment*, problems with mental functions;
- *Executive dysfunction*, problems with the executive system (the bodily system that controls and manages other cognitive processes such as goal directed behavior and managing more complex tasks).

However, apathy in patients with PD is less likely to be associated with:

- Severity of motor symptoms;
- Dosage of the antiparkinson medication, *levodopa* (L-dopa);
- Level of physical disability;
- Duration or length of PD.

The impact of apathy is significant, leaving patients generally inactive. This increased passivity leads to further functional decline and greater debility, which families often inaccurately attribute to laziness, entitlement, or disobedience. This tendency for patient family members and caregivers to associate signs of apathy with negative personality traits can lead to resentment, especially when apathy remains undiagnosed.

Clinical Features of Fatigue in PD:

Fatigue can be classified into two main categories:

- Peripheral: A functional abnormality involving an extreme lack of energy due to muscular exhaustion. This category of fatigue is measured by observing:
 - Decreased ability to generate force;
 - Inability to sustain repetitive movements.
- Central: An abnormal degree of persistent tiredness, weakness or exhaustion that occurs in the absence of motor or physical impairment. This type of fatigue is a subjective experience that can belong to one (or both) of two subtypes:
 - Physical fatigue: The sensation of physical exhaustion and lack of energy to perform physical tasks, despite the ability to do so;
 - Mental fatigue: The effects felt during and after long periods of demanding cognitive activities that require constant mental use.

Given its subjective nature, the overlap between physical and mental fatigue is not always clear. However, by definition, *mental fatigue* is fatigue that involves problems initiating and maintaining activities mediated by thinking skills.

Fatigue has adverse affects on quality of life, depression and disability in PD. It is also the primary determining factor of work-related disability. In interviews of patients with PD, patients described fatigue as unpredictable in terms of:

- Onset;
- Duration;
- Relationship to prior activity.

Patients also said that fatigue seems to be aggravated by physical, psychological or social stressors. In patients with PD, fatigue is associated with higher rates of depressive symptoms, sleep disturbances and cognitive disorders. However, it is also highly prevalent in non-depressed patients. One study reported that 43% of PD patients without depression, dementia, or sleep problems still reported fatigue.

Conversely, the relationship between fatigue and PD motor symptoms, daytime sleepiness, sleep quality and physical activity still remains inconsistent. In addition, fatigue appears to be unrelated to exercise efficiency, activity level or physical tiredness.

Diagnosis, Assessment and Classification of Apathy & Fatigue in PD:

Both apathy and fatigue are difficult to diagnose due to:

- Their tendency to occur in the presence of coexisting mood symptoms and cognitive deficits;
- Their overlap with PD motor signs.

Diagnosis, Assessment and Classification of Apathy in PD:

The diagnosis of apathy can also be challenging because the definition of apathy varies in medical literature and no standardized or validated criteria or official clinical diagnosis for apathy exists.

Currently, both *Marin's criteria of reduced goal-oriented behavior and cognition* and *Marin's criteria for emotional concomitants of goal-directed behavior* are the most widely used. However, it is difficult to apply these criteria in PD due to controversy over their added emotional dimension and their inclusion of cognitive deficits.

When used with a follow-up diagnostic interview, clinical rating instruments are generally helpful as apathy screening tools. However, the rater (i.e. patient, caregiver, or clinician) influences the quality of the information obtained. For example, patients with apathy may be indifferent as to whether they have

experienced behavioral changes, but in order to distinguish apathy from depression, patients must exhibit signs of emotional features (ex. low mood, reduced sense of pleasure, guilt, diminished self-attitude, etc.).

Diagnosis, Assessment and Classification of Fatigue in PD:

The diagnosis of fatigue is also challenging because fatigue is an independent symptom that can also be a feature of other disturbances. For example, fatigue is one of the criteria for diagnosing major depression, yet it can be challenging to identify fatigue as a stand-alone entity due to symptoms of depression.

Nevertheless, a number of fatigue rating scales have been developed for the general population, as well as for specific conditions, to help identify this syndrome.

Management of Apathy & Fatigue in PD:

To best manage apathy and fatigue, the following elements are key:

- Careful attention and watchfulness for the signs and features of each symptom;
- Use of informants to obtain data for establishing clinical identification;
- Appropriate use of assessment tools to screen for the presence of non-motor symptoms.

When it comes to treating both apathy and fatigue in PD, researchers also stress the importance of providing illness education to families and patients about:

- Depression, fatigue, apathy and cognitive disturbances in PD;
- Behavioral strategies used to maximize *executive functions*, or brain processes that guide thought and behavior related to internal goals or plans;
- Use of medications to treat mood disorders and cognitive disturbances.

These points are especially important because improvements in coexisting conditions may be enough to relieve or at least improve apathy and fatigue when they do occur.

Management of Apathy in PD:

Unfortunately, studies on specific treatments for apathy in PD are limited. Furthermore, the management of apathy in PD is often difficult because patients are indifferent to the importance of tending to their own health and well-being. As of yet, drug-based medications for the treatment of apathy in PD include:

- Stimulants;
- *Modafanil*, a wake-promoting drug;
- *Dopamine antagonists*, drugs that blocks dopamine receptors;

- *Testosterone*, a steroid hormone used to treat various disorders.

Alternately, non drug-related treatment strategies include providing a personalized daily schedule with different group activities and group experiences that help to maintain a good level of activity and enrichment. Also important is the role of family as a therapeutic resource.

Management of Fatigue in PD:

Likewise, few studies have investigated the management of fatigue. However, on reviewing existing studies, researchers highlighted the following findings on the treatment of fatigue in PD:

- In several clinical trials, *methylphenidate* (Ritalin; a mild stimulant) had a favorable effect on general fatigue, and the antiparkinson medication *levodopa* (L-dopa) had improved physical fatigue.
- In another study, dopamine antagonists were only helpful in improving fatigue for some PD patients, whereas fatigue worsened in the study's placebo group (the group that did not actually receive the medication) compared to those who initiated L-dopa therapy early in the course of PD.
- In one trial, *Modafanil* improved excessive daytime sleepiness but not fatigue in PD, whereas nocturnally administered *sodium oxybate* (a therapeutic drug used to treat fatigue, clinical depression and narcolepsy) improved both excessive daytime sleepiness and fatigue in PD.

Hallucinations & Psychosis in PD

Hallucinations and psychosis in PD are closely related. Researchers defined these neuropsychiatric symptoms as:

- Hallucinations: Abnormal perceptions that occur in the absence of a physical stimulus and which may involve any sensory dimension (i.e. visual, auditory, tactile, etc.).
- Psychosis: The full spectrum of features seen in PD-related mental illness, including hallucinations and delusions, as well as “milder” incidences like illusions and sense of presence.

Thought disorders, such as delusions, are primary features of psychosis that may appear in some patients with PD. However, psychotic symptoms may also appear in “milder” forms, such as:

- Visual hallucinations (VH);
- *Illusions*, misperceptions of real stimuli that are often visual in nature;
- *Passage hallucinations*, fleeting, vague images in the peripheral (side) vision;
- *Presence hallucinations*, the experience that someone is present when no one is actually there.

These psychotic symptoms may be minor or serious, occur together or alone, be accompanied by emotional and behavioral disturbances, and/or require psychiatric hospitalization. Furthermore, even though studies on psychosis generally focus on visual hallucinations, which are the most common type of psychotic symptoms in PD, hallucinations can also occur in all sensory domains, such as auditory or *tactile* (touch).

Prevalence and Pattern of Occurrence:

According to researchers, psychotic symptoms frequently occur in PD and can have a substantial impact on patients. The frequency of psychotic symptoms in PD varies according to the definition used. If milder forms of psychosis are included, psychotic symptoms may affect up to 50% of patients with PD. Yet, because relatively few long-term studies of PD exist and psychotic symptoms tend to be persistent and progressive, these symptoms in PD have not been observed over time. Thus, it is crucial to identify and track the course of psychotic symptoms in order to provide the best management for PD patients.

Clinical Features of Hallucinations and Psychosis in PD:

Visual hallucinations (VH), which are the most common psychotic symptom in PD, typically consist of persons (familiar and/or unfamiliar) but sometimes consist of animals or objects. Other common features of VH are that:

- They usually occur alone or few in number, but they can be numerous as well;
- They are typically complex and appear in a stereotypical form that is subjective to the patient;
- They appear abruptly, move often, and usually seem very real;
- They vanish suddenly, sometimes when the patient tries to approach or touch them, or when the patient asks for other people to confirm the existence of the VH;
- They occur in dim light or at night.

Misidentification episodes may also occur, such as *capgras*, a disorder where a person holds a delusional belief that someone they know has been replaced by an identical looking imposter. Typically, the patient thinks that his or her spouse is someone else and not the real partner, which may result in emotional or behavioral changes. Other forms of delusions are relatively rare, but they are often accusatory or focus on infidelity.

Diagnosis, Assessment and Classification of Hallucinations & Psychosis in PD:

In order to properly assess and diagnose psychosis in PD, researchers strongly recommend that clinicians take the following measures:

- Be sure to ask patients if any psychotic episodes have occurred, since psychotic symptoms are not always willingly reported;
- Be sure to question the patient's caregiver of any symptoms of psychosis, since some patients may deny or refuse to report symptoms or even forget to do so (as in dementia);
- Make sure to note the frequency, intensity and impact of the symptoms, as well as:
 - The situation and the circumstances in which they occur;
 - Details and specifics of the way the patient perceives and interprets the psychotic episode(s);
 - Any other accompanying symptoms, such as cognitive impairment, depression, anxiety or sleep disorders.

Management of Hallucinations & Psychosis in PD:

Non Drug-Related Treatment:

Non drug-related options for managing psychosis include:

- Using an educative approach, such as providing patients and caregivers with information and guidance about the nature of the illness;
- Using a cognitive-behavioral approach, such as distraction or re-directing attention from the disease;
- Using environmental interventions, such as improving light-conditions and visual aids;
- Looking for potential medical factors that may contribute to psychotic episodes, such as:
 - Pain;
 - Infection;
 - Dehydration;
 - Disturbances in normal metabolism;
 - Sensory deficits;
 - Recent changes in medication.

Drug-Related Treatment:

Alternately, when it comes to drug-related treatments for hallucinations and psychosis in PD, the first step is to adjust or modify the anti-Parkinson's medication already being taken. This is because reducing the dosage or the number of drugs may lessen the severity of symptoms, even without worsening motor symptoms. Afterwards, researchers strongly recommend taking the following steps:

1. According to expert opinion, *anticholinergics* (or medications that inhibit brain activity related to the chemical acetylcholine) should be withdrawn first.
2. Then it is usually recommended to withdraw the anti-Parkinson's medications *selegine*, *amantadine*, and dopamine antagonists before changing L-dopa dosage.

So far, the antipsychotic *clozapine* is the only adequately tested drug recommended to patients, reportedly improving VH without worsening motor symptoms. However, it should be noted that the clinical trials testing *clozapine* have been conducted only in PD patients without dementia.

Researchers also found that the anticholinergic drug *rivastigmine* seems to be particularly useful in PD with VH, helping to reduce patient cognitive decline. However, antipsychotics such as *risperidone* and *olanzapine* are less useful in treating PD-related psychosis since they were reportedly less effective and had a higher risk of adverse effects, including:

- The worsening of motor symptoms;
- Cognitive decline;
- Drowsiness;
- Confusion.

When treating patients with psychosis and hallucinations in PD, careful monitoring of medications is necessary and dosage should be low and given in small increments due to potential adverse side effects or adverse events.

Conclusion

Neuropsychiatric symptoms in PD are complex mental disorders that have a significant impact on many Parkinson's patients, as well as their caregivers and families. While much progress has been made in researching these symptoms, characterizing their individual features and observing their effect on patients, proper diagnosis and management of these disorders remains an obstacle for many clinicians.

Unfortunately, the complexity of PD makes diagnosing and treating these symptoms even more problematic, since clinicians must account for symptom overlap, make diagnoses using inadequate assessment tools and choose from treatments that are often inconclusive in terms of effectiveness. Thus, to best deal with current diagnostic obstacles, validated criteria must be established for each neuropsychiatric symptom by either modifying existing criteria for increased PD-compatibility or by

formulating new criteria. Moreover, to improve the management of these disorders, well-designed, large-scale, long-term, placebo-controlled studies must be conducted on existing treatments (both drug-related and non drug-related) in order to validate their effectiveness and determine their impact/benefit on each symptom.