Nonmotor Symptom Complex of Parkinson’s Disease – An Under-recognized Entity

Manmohan Mehndiratta*, Rohit K Garg†, Sanjay Pandey‡

Abstract
Parkinson’s disease (PD) is the second most common neurodegenerative disorder, after Alzheimer’s disease. The cardinal clinical features of PD include asymmetric onset of bradykinesia, rigidity, and resting tremor. Most patients of idiopathic PD present with one or more of the cardinal motor features. Apart from these, various nonmotor symptoms (NMS) also occur in PD and constitute a major clinical challenge, as they are common, but often overshadowed by the dominance of motor symptoms. NMS can present at any stage of the disease including early and pre-motor phase of PD. Several NMS such as olfactory dysfunction, constipation, REM behaviour disorder, depression may antedate the motor signs, symptoms and diagnosis of PD by a number of years. Since, NMS add significantly to the overall disability caused by PD, their early recognition and treatment may go a long way in improving the quality of life of PD patients as well as the economic burden on the carers. The identification of NMS can be improved by the application of quantitative and validated instruments and scales for their assessment.

Introduction
Parkinson’s disease (PD) is the second most common neurodegenerative disorder, after Alzheimer’s disease. James Parkinson is attributed with rendering the first description of PD in his monograph, *The Shaking Palsy* (1817). He identified the hallmark features of the illness through cases observed in the streets of London as well as his own patients. In community-based series, PD accounts for more than 80% of all Parkinsonism, with a prevalence of approximately 360 per 100,000 and an incidence of 18 per 100,000 per year. Among the subjects with Parkinsonism visiting the movement disorder clinics, approximately 80-85% have PD, the rest belonging to the categories of atypical Parkinsonism and secondary Parkinsonism. PD afflicts approximately one million individuals in the United States (~ 1% of those over 55 years). Another study reported that about 1% of population above the age of 65 years and about 5% above the age of 80 years suffer from PD. It can, therefore, be calculated that in India alone with an estimated population of over one billion by the turn of the century, approximately 700 million people will be above the age of 65 years, of which about 7 million will suffer from PD.

The cardinal clinical features of PD include asymmetric onset of bradykinesia, rigidity, and resting tremor. The peak age of onset of PD is in the early 60s (range 35-85 years), and the course of illness ranges from 10 to 25 years. These are the consequences of the loss of dopaminergic neurons in substantia nigra pars compacta. Dopamine deficiency in the nigro-striatal pathways in parkinsonian brain homogenates was described by Ehringer and Hornykiewicz (1960), a discovery that ultimately led to highly effective pharmacotherapy with levodopa and direct-acting dopamine agonists.

Nonmotor Symptoms of Parkinson’s Disease
Most patients of idiopathic PD present with one or more of the cardinal motor features. Apart from these, various nonmotor symptoms also occur in PD and constitute a major clinical challenge, as they are common, but often overshadowed by the dominance of motor symptoms. The nonmotor symptoms (NMS) of PD were also recognised by James Parkinson, who referred to sleep disturbance, constipation, dysarthria, dysphonia, dysphagia, sialorrhoea, and urinary incontinence in his ‘Essay on the shaking palsy’ in 1817. Since then, numerous studies have indicated that nonmotor symptoms are frequent accompaniments of PD (Table 1), and can significantly impair quality of life, and may precipitate hospitalisation.

The Problem Statement
The prevalence of nonmotor symptoms (NMS) of PD as a whole is inadequately documented because there are insufficient adequately powered, community-based studies on prevalence, effect, and treatment efficacy in relation to the nonmotor symptoms, and there is a need for large and well-designed prospective studies.

Despite their impact on quality of life, the NMS of PD are not well recognised in clinical practice. One of the studies reported that existing depression, anxiety and fatigue are not identified by neurologists in over 50% of consultations, and sleep disturbance in over 40%. Another study attempted to correlate nonmotor symptoms in PD at presentation retrospectively after clinico-pathological confirmation of diagnosis. 21% had NMS at presentation and these included pain, anxiety, urinary dysfunction and depression. Some of these patients were more likely to be misdiagnosed initially and had inappropriate medical interventions. It is a common misconception that NMS occur only in late or advanced PD. NMS can present at any stage of PD including the early and pre-motor phase. Prospective data based on the Honolulu Asia ageing and other studies suggest

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that several NMS of PD such as olfactory problems, constipation, depression and erectile dysfunction may antedate the motor signs, symptoms and diagnosis of PD by a number of years.9,18 It has been suggested that some NMS such as olfactory dysfunction in combination with others like rapid eye movement behaviour disorder (RBDS) or constipation may be useful to identify a population “at risk of PD”, which will be particularly important if and when neuroprotective therapies become available (Table 2).17

Stacy et al. reported that NMS were present even in patients within 5 years of (motor) disease onset, and these were identified frequently with the use of a patient-completed questionnaire.19 Recent studies using the nonmotor questionnaire for PD (NMSQuest) have also highlighted the significant occurrence of 30 different NMS in PD in comparison to an age-matched control group (Table 3).7 Irrespective of the disease stage, up to 9-12 different NMS may be unmasked in most PD patients by the use of the NMSQuest at clinic visit.7 The recently published PDLIFE study highlighted the issue that a decision to delay treatment for PD is usually based on assessment of motor state alone, while the major deterioration may be in several nonmotor domains of PD. Therefore, in the present era, attention is being focussed on the recognition and quantification of nonmotor symptoms, which will form the basis of improved treatments.
The Spectrum of Non-Motor Symptoms in Parkinson’s Disease

Sleep Disturbances

Sleep disorders are among the most frequent nonmotor problems of PD. They include difficulties falling asleep, frequent awakenings, nocturnal cramping, painful dystonia, or nocturnal motor symptoms with difficulties turning in bed, restless legs syndrome (RLS), night-time incontinence, nocturnal hallucinosis, and daytime sleepiness.

**REM sleep behaviour disorder (RBD)**

RBD is a parasomnia characterised by loss of normal skeletal muscle atonia during REM sleep, thus enabling patients to physically enact often vivid and unpleasant dreams. RBD occurs in about a third of patients with PD and may precede the development of motor symptoms in over 40% of patients. Vocalisations (talking, shouting, vocal threats) and abnormal movements (arm or leg jerks, falling out of bed, violent assaults) are commonly reported by bed partners.

Imaging studies in patients with isolated RBD, have indicated a small but significant symmetrical reduction in striatal dopaminergic uptake, which may be suggestive of preclinical PD. The pathological basis of RBD is unknown. It is suggested that that RBD may arise due to the degeneration of lower brainstem nuclei including the pedunculopontine and subcoeruleal nucleus areas affected in Braak stages 1 and 2.

**Excessive daytime sleepiness**

Excessive daytime sleepiness (EDS) and involuntary dozing affects up to 50% of PD patients and may also be preclinical marker for PD. Neuronal degeneration in suprachiasmatic nucleus that regulates the internal diurnal rhythm may be implicated, while hypocretin (orexin), a hypothalamic peptide may also have a regulatory role. The involvement of these areas in Braak stages 1 and 2 may explain the early occurrence of EDS. A combination of the disease process, the effect of nocturnal sleep disruption, and antiparkinsonian drugs (dopamine agonists and levodopa) is probably causative.

**Restless legs syndrome (RLS)**

RLS symptoms are often reported in PD, but prevalence studies of RLS in PD are few with inconsistent results. Underlying pathophysiology potentially shared by RLS and PD is mainly suggested by the similarities in treatment response. Some authors have reported subtle deficits in nigrostriatal terminal function based on the functional imaging studies in RLS. Further long-term studies will clarify whether or not RLS is associated with an increased risk for development of PD.

**Neuropsychiatric symptoms**

Psychiatric syndromes as well as cognitive impairment frequently complicate PD. Development of psychopathology in PD is attributed to a number of factors, including underlying disease processes related to PD, medication effects, and psychological reactions to the illness. Up to 90% patients experience psychiatric complications, including major mood disorders (major depression, dysthymia, or bipolar disorder), adjustment disorders, anxiety syndromes, drug-induced mood changes, pathological tearfulness, dementia, apathetic states, psychosis, or delirium.

**Depression**

The prevalence of major depression in PD is estimated to be 40%, with reported prevalence rates ranging from 4% to 70%. Major depression accounts for about half of the cases with significant depression, whereas others experience adjustment disorders, dysthymia, or bipolar disorder. The major depressive syndrome is frequently accompanied by anxiety symptoms.

The diagnosis of depression in PD can be difficult because of the overlap between depressive features and the symptoms

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Table 3: PD NMS Questionnaire* (The 30-item screening questionnaire for PD [NMSQuest])

<table>
<thead>
<tr>
<th>Number</th>
<th>Question</th>
<th>YES……. NO……</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dribbling of saliva during the daytime</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>2.</td>
<td>Loss or change in your ability to taste or smell</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>3.</td>
<td>Difficulty swallowing food or drink or problems with choking</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>4.</td>
<td>Vomiting or feelings of sickness (nausea)</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>5.</td>
<td>Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>6.</td>
<td>Bowel (faecal) incontinence</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>7.</td>
<td>Feeling that your bowel emptying is incomplete after having been to the toilet</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>8.</td>
<td>A sense of urgency to pass urine makes you rush to the toilet</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>9.</td>
<td>Getting up regularly at night to pass urine</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>10.</td>
<td>Unexplained pains (not due to known conditions such as arthritis)</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>11.</td>
<td>Unexplained change in weight (not due to change in diet)</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>12.</td>
<td>Problems remembering things that have happened recently or forgetting to do things</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>13.</td>
<td>Loss of interest in what is happening around you or doing things</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>14.</td>
<td>Seeing or hearing things that you know or are told are not there</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>15.</td>
<td>Difficulty concentrating or staying focussed</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>16.</td>
<td>Feeling sad, low or blue</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>17.</td>
<td>Feeling anxious, frightened or panicky</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>18.</td>
<td>Feeling less interested in sex or more interested in sex</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>19.</td>
<td>Feeling it difficult to have sex when you try</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>20.</td>
<td>Feeling light headed, dizzy or weak standing from sitting or lying</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>21.</td>
<td>Falling</td>
<td>YES……. NO……</td>
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<tr>
<td>22.</td>
<td>Finding it difficult to stay awake during activities such as working, driving or eating</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>23.</td>
<td>Difficulty getting to sleep at night or staying asleep at night</td>
<td>YES……. NO……</td>
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<tr>
<td>24.</td>
<td>Intense, vivid dreams or frightening dreams</td>
<td>YES……. NO……</td>
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<tr>
<td>25.</td>
<td>Talking or moving about in your sleep as if you are ‘acting’ out a dream</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>26.</td>
<td>Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move</td>
<td>YES……. NO……</td>
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<tr>
<td>27.</td>
<td>Swelling of your legs</td>
<td>YES……. NO……</td>
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<tr>
<td>28.</td>
<td>Excessive sweating</td>
<td>YES……. NO……</td>
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<tr>
<td>29.</td>
<td>Double vision</td>
<td>YES……. NO……</td>
</tr>
<tr>
<td>30.</td>
<td>Believing things are happening to you that other people say are not true</td>
<td>YES……. NO……</td>
</tr>
</tbody>
</table>

*Adapted from Chauduri et al. (2006)
of PD itself. Accordingly, PD can be misdiagnosed as a primary depressive illness, and concomitant depression may go unrecognized in the PD patient. Even when both conditions (PD and depression) are diagnosed concurrently, it can be difficult to tease apart which clinical phenomena are related to primary motor vs. primary psychiatric pathology (Table 4).41

A central issue is whether the major depressive syndrome in PD is a reaction to the motor disability or whether the syndrome is intrinsic to the disease processes of PD. Research examining the theory that depression is integral to disease process has evaluated the impact of disease severity, disease duration, age of onset, and gender on depression, with no consistent relationship found between these variables and depression.42 The evidence that depression can precede the development of motor symptoms also suggests that depression in itself is a neurological symptom of PD.43 Other studies suggest that depression is a reaction to the disability, on the basis of correlations between depression severity and motor impairment.44 Clearly, the relationship between mood and motor phenomena in PD is complex. Further research examining the factors associated with depression in PD, especially how it relates to disability and functional status, is needed.50

Anxiety

Anxiety is a common problem in PD, but has gained relatively little attention. While anxiety can present as an isolated symptom or as a feature of depression, clinically significant anxiety syndromes occur in up to 40% of PD patients.45 Particularly common are generalized anxiety disorder, social phobia, and panic disorder, which have a prevalence rate of 25% in some series.46,47 These syndromes may also precede or accompany a major depressive syndrome, and should be regarded as distinct from anxiety, which is an understandable psychological response to motor impairment or other personal concerns.

Symptoms of autonomic dysfunction can also be associated with anxiety or depression. Accordingly, somatic complaints related to autonomic symptoms (e.g., flushing, dizziness, urinary frequency, or changes in heart rate) must be evaluated carefully because they can be misdiagnosed (and mistreated), as if they represented affective syndromes.48 The anxiety syndromes in PD appear related to underlying brain disease, with evidence implicating noradrenergic dysfunction.49,50 Several studies have reported that anxiety syndromes may even precede the onset of motor symptoms of PD.51

Psychosis

Hallucinations and delusions occur in up to 40% of PD patients and are a major precipitant of nursing home placement.52 Psychosis is related to dopaminergic medications in about 20% of PD patients,53 a relationship that tends to overshadow other important causes of psychosis in PD. Psychosis can also develop spontaneously or in association with cognitive impairment, on-off fluctuations, mood disturbance, other psychoactive medications, and/or delirium.54

The psychotic syndromes are frequently categorized into three general groups:55

The first group consists of visual hallucinations (vivid depictions of animals or people) occurring in a clear sensorium and accompanied by insight. The second type generally involves more persistent hallucinations or delusions in a clear sensorium but with diminished insight. This state often requires definitive antipsychotic treatment. In the third group, hallucinations or delusions occur in the context of a delirium. A population-based study of psychosis showed associations among psychotic symptoms and age, stage, and diagnostic subgroup of PD, severity of depression, and cognitive impairment, whereas antiparkinsonian medications did not discriminate between the PD patients with and without psychosis.56 This finding suggests more widespread pathologic brain involvement in the setting of psychosis and argues against a prominent role for antiparkinsonian medicines in the development of psychosis.

Cognitive impairment

Dementia occurs in up to 40% of people with PD, a rate about six-times higher than that in healthy individuals.60 It is clinically characterised by a dysexecutive syndrome with impairment of visuospatial abilities and memory on a background of loss of response to dopaminergic drugs including levodopa.61 Degeneration of nigral cells is implicated, and although presence of cortical and subcortical Lewy bodies is also likely to be causative, this is controversial.62 Cholinergic cell loss in the nucleus basalis of Meynert is prominent in PD and forms the basis of cholinergic treatment for dementia in the disease. The contribution of comorbid Alzheimer’s disease and vascular pathology, as well as a possible genetic association with the APOE genotype, have also been implicated.63 About 25% of patients develop an Alzheimer-type dementia with cortical features of aphasia, apraxia, and memory deficits.64 While depressive disorders can coexist with dementia in PD, families and clinicians may also misinterpret a tendency to reduce social interactions in early dementia as a sign of depression rather than impaired cognition only and seek antidepressant treatment. The distinction is important, since PD patients with dementia are especially vulnerable to psychoactive medication effects and the development of delirium, a leading cause of nursing home placement in PD.65

Dysautonomia

Autonomic dysfunction is an almost universal feature of PD and includes orthostatic hypotension (OH), constipation, urinary and sexual dysfunction.66 The pathophysiology is complex and includes degeneration and dysfunction of the nuclei mediating autonomic functions such as dorsal vagal nucleus, nucleus ambiguus, and other medullary centres, which exert differential control on the sympathetic preganglionic neurons via descending pathways.67 Additionally, degeneration of cholinergic, monoaminergic, and serotoninergic nuclei cause abnormalities within the central autonomic network.68

A study of 141 patients with PD and 50 healthy age-matched controls showed that the prevalence of orthostatic dizziness, constipation, bladder dysfunction, erectile dysfunction, and hyperhidrosis was significantly higher than in controls and 50% of patients with PD rated their effect on daily living as “a lot” or “very much.”69 A recent study reported that autonomic symptoms were significantly more common across all stages
Autonomic function in PD can be objectively assessed by several validated tests, including QSART (quantitative sudomotor axon reflex test for sudomotor function), urodynamic studies such as uroflowmetry and cystometry for bladder dysfunction, defeating proctography (bowel dysfunction), 60 degrees head-up tilt test with cardiovascular monitoring (postural hypotension), sympathetic skin response, and pupil function tests with pilocarpine or phenylephrine. In cases where distinction from multiple system atrophy or other causes of primary dysautonomia is needed, tests such as urethral sphincter electromyography, catecholamine concentrations (plasma norepinephrine concentrations) in response to head-up tilting, and clonidine-induced growth hormone challenge tests could be useful.

**Sensory Symptoms and pain**

Sensory symptoms in PD have been described as numbness, tingling, burning, aching, coldness, heat, and pain. James Parkinson himself noted “rheumatic pain” ipsilateral to the extremity first affected by rest tremor, and Charcot noted it in his lectures on cramps, muscular aching, rheumatoid and neuralgic pains experienced by patients with PD. Other series have reported such primary sensory symptoms in 40% - 50% of patients. Table 5 shows the frequency of various sensory symptoms experienced by a series of 50 PD patients. Pain may be related to motor fluctuations, early morning dystonia, or secondary causes such as musculoskeletal pain. Several authors have noted painful sensations as the presenting symptom of PD. Spontaneous limb pain in PD is often reported as proximal and more prominent in the limb first and more severely affected.

The pathophysiology underlying sensory symptoms and pain in OD is poorly understood. There is evidence that pain is probably a result of altered central pain processing as part of the neurodegenerative process. Possible explanations include loss of dopaminergic, pain-inhibiting descending input to dorsal horn synapses due to substantia nigra or ventral tegmental dopaminergic cell loss. Dopaminergic denervation could also potentially induce central hypersensitivity to pain stimuli via basal ganglia-thalamic connections. Non-dopaminergic mechanisms could also be involved – loss of noradrenergic descending pain inhibitory input from locus ceruleus to dorsal horn of spinal cord. It has also been reported that the widespread cortical Lewy body degeneration also can affect areas of central pain processing system, including the cingulate gyrus, insular cortex, amygdala, and hypothalamus.

**Table 5: Frequency of sensory symptoms in Parkinson’s disease**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%) (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tightening sensation</td>
<td>42</td>
</tr>
<tr>
<td>Tingling sensation</td>
<td>38</td>
</tr>
<tr>
<td>Diffuse pain</td>
<td>36</td>
</tr>
<tr>
<td>Neuralgic pain</td>
<td>18</td>
</tr>
<tr>
<td>Burning sensation</td>
<td>8</td>
</tr>
</tbody>
</table>

*Adapted from Witjas et al. (2002)*

of PD. Significant peripheral sympathetic failure is rare in PD and clinically leads to orthostatic hypotension, which usually develops late in the disease, unlike in multiple system atrophy where it is an early manifestation.

**Orthostatic hypotension**

One of the retrospective reviews of 135 cases of pathologically proven PD reported evidence for symptomatic orthostatic hypotension (OH) in 30%, bladder dysfunction in 32%, and constipation in 36%. In another study, the tilt-table testing detected OH in 58% patients. In 20%, OH was symptomatic and correlated with dopaminergic medication dose and duration and severity of PD. Peripheral sympathetic cardiovascular denervation has been implicated as the mechanism of OH in PD, as shown in various studies.

**Constipation**

Constipation is one of the commonest nonmotor symptoms in PD. Several case control studies have reported increased prevalence of constipation in PD of between 28% and 61% compared to control cases (6%-33%). One study reported either constipation or prolonged intestinal transit time in as many as 80% of patients with PD. Constipation has been reported as a prominent complaint prior to the onset of motor symptoms of PD in about 50% of patients in one series. Lewy body pathology in the peripheral autonomic nervous system involving the myenteric plexus with subsequent colonic sympathetic denervation contributes to constipation in PD.

**Sexual dysfunction**

Sexual dysfunction in PD may manifest as both reduced and abnormally increased sex drive. Erectile and ejaculatory function may occur. Testosterone deficiency has been implicated. Yu and colleagues noted that 17 of 21 male patients with PD had substantial impairment of sexual arousal, behaviour, drive, and orgasm domains, whereas in those with longer duration of the disease sexual fantasy was increased. Another study reported high prevalence (76.5%) of sexual dysfunction in patients after bilateral subthalamic nucleus stimulation. Aberrant sexual behaviour may also occur as part of dopamine dysregulation syndrome, due to dopaminergic drug treatment in susceptible patients.

**Urinary dysfunction**

This may include urinary frequency and urgency, incomplete bladder emptying, double micturition, and urge incontinence. The most common abnormality is related to detrusor hyperreflexia, while detrusor hypoactivity seems to be less prominent. Paradoxical co-contractions of urethral sphincter muscle has also been described.

Urological examination and urodynamic investigations are mandatory to correctly identify the type of dysfunction underlying the patient’s bladder problem and initiate appropriate treatment.
the olfactory bulb and anterior olfactory nucleus, and resultant olfactory disturbance as a preclinical or motor symptom. They also underscore the potential of olfactory function testing as a screening tool for persons at risk for PD.

### Recognition of Nonmotor Symptoms

The nonmotor symptoms of PD are frequently overlooked. In a prospective study of 101 patients, the physician did not discuss important symptoms such as depression, anxiety, fatigue, and sleep disturbance with more than 50% of their patients. This finding was attributed to the following possibilities:

- Limited consultation time
- Perception of the patient and the carer that their symptoms are unrelated to the disease (e.g., visual hallucinations or diplopia)
- Non-awareness of the physician who may target only the motor symptoms of PD
- An expectation that non-motor symptoms will be managed in the community, usually by the family doctor or community health nurse.

However, even though the physician might not always actively treat the nonmotor symptoms, he or she might be best qualified to identify them, especially as they can often be difficult to diagnose. For example, depression may be missed (or overdiagnosed) in a patient with bradyphrenia and mask-like face, and experience is required to differentiate drug-induced and degenerative psychosis. The identification of nonmotor symptoms can be improved by the application of quantitative and validated instruments for their assessment; for e.g., Epworth sleepiness scale (for sleep disorders), Hospital quantitative and validated instruments for their assessment; screening tool for persons at risk for PD.

### Conclusion

The nonmotor symptoms are universal features of idiopathic PD. They add significantly to the overall disability caused by PD and are the critical determinants of health related quality of life of affected patients. In the presence of effective symptomatic therapies for the motor symptoms of PD, the nonmotor symptoms have become major prognostic factors for overall disease burden and everyday function in PD. Furthermore, there is evidence that many nonmotor symptoms may antedate the onset of motor symptoms of PD by years or even decades and may thus turn out to be a critical target for early diagnosis and identification of at-risk populations. Early recognition and treatment of nonmotor symptoms may go a long way in improving the quality of life of PD patients as well as the economic burden on the carers.

### References


