Burden of non-motor symptoms of Parkinson's disease

Mary G Baker and Jill GC Rasmussen

Introduction and background

In an overview of Parkinson's disease (PD), Burn1 noted that there had been little change in the description of the clinical features of PD since James Parkinson's seminal account in 1817.2 He summarised the "shaking palsy" ("paralysis agitans") as “…involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.” In his graphic description of the natural history of the untreated disease he traces the inexorable decline that characterises his namesake disease.

The focus on the motor components of PD together with its neurological aetiology and consequent clinical management has largely overshadowed the prevalent non-motor symptoms. Only in the last decade and particularly with publication of the Global Parkinson's Disease Survey3 has the clinical view of PD begun to appreciate the impact of non-motor symptoms on the quality of life (QoL) not only of patients, but also their ‘informal’ carers and the consequent socio-economic costs.

Appreciation of the importance of non-motor symptoms for patients with PD does, however, bring to the clinician a much more complex diagnostic and management problem. First, non-motor symptoms are often more difficult to detect than the classical motor signs. Parkinson's disease patients often seem unaware or are reluctant to mention that the problems mainly disturbing them are not motor symptoms. Second, motor symptoms of PD overlap and may overshadow common non-motor symptoms such as depression. Third, there is no single screening instrument that covers the whole range (Table 1) of non-motor symptoms. Optimal treatment of patients with PD will require detection of non-motor symptoms and this will in turn require acute attention both to what the patient says and to what he or she does not say.

Having detected non-motor symptoms, there remains the problem of management. With few exceptions, the drugs prescribed for healthy adults with similar symptoms have not been tested in patients with PD and their effectiveness in this population is largely undocumented. This has led the UK National Institute for Health and Clinical Excellence (NICE) to call for well-conducted studies to provide evidence to support recommendations for specific interventions for the various non-motor symptoms.4

It should be noted that the frequent association of anxiety, depression and other non-motor symptoms of PD does not prove that these are actual symptoms of PD arising from the same neurological insults that underlie motor symptoms. This rather academic distinction does not relieve clinicians of their responsibility to manage all aspects of the PD patient’s disease, but does mean that neurological interventions may not optimally address non-motor symptoms.
Non-motor symptoms such as anxiety, depression, and REM sleep disorder may present before motor symptoms are manifest. It is certainly not proven, but possible that such symptoms are in some cases prodroma to PD. It is known that the nigrostriatal system is remarkably plastic and that 80% of dopaminergic neurons are lost before classical motor symptoms appear, suggesting a relatively long preclinical phase of disease. Whilst some studies suggest a short preclinical phase, the relatively slow rate of decline for most patients following diagnosis would suggest otherwise and the concept of the ‘PD Personality’ suggests a much longer preclinical phase.

Whether or not non-motor symptoms precede the classical signs of PD, most patients with a diagnosis of PD will be troubled by non-motor symptoms that:

- Correlate with increasing age and severity of PD although non-motor symptoms, particularly depression, have much greater negative impact on patients’ QoL.
- Are often the most disabling features of PD.
- Best predict deterioration of patients’ QoL, disability, institutionalisation, and shortened life expectancy.
- Have serious negative effects upon the health and QoL of ‘informal’ carers who are often elderly, infirm and economically stressed.

### Table 1. Overview of non-motor symptoms in Parkinson’s disease

<table>
<thead>
<tr>
<th>Neuropsychiatric</th>
<th>Sleep disorders</th>
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<tr>
<td>Anxiety, panic attacks</td>
<td>Restless legs</td>
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<td>Apathy, anhedonia</td>
<td>REM and non-REM sleep behaviour</td>
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<tr>
<td>Confusion</td>
<td>Excessive daytime sleepiness</td>
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<tr>
<td>Dementia</td>
<td>Insomnia</td>
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<td>Depression</td>
<td>Sleep apnoea</td>
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<td>Fatigue</td>
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<td>Hallucinations</td>
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<tr>
<th>Autonomic</th>
<th>Gastrointestinal</th>
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<tr>
<td>Dry eyes/mouth</td>
<td>Ageusia</td>
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<tr>
<td>Postural hypotension</td>
<td>Excessive dribbling</td>
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<tr>
<td>Seborrhoea</td>
<td>Constipation</td>
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<tr>
<td>Sexual dysfunction</td>
<td>Dysphagia</td>
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<tr>
<td>Sweating</td>
<td>Nausea, vomiting</td>
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<td>Urinary dysfunction – frequency, nocturia, urgency</td>
<td>Weight loss</td>
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<th>Sensory</th>
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<td>Olfactory disturbance</td>
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<td>Pain</td>
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<td>Parasthesiae</td>
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REM, rapid eye movement
Although the burden of PD on patients, their ‘informal’ carers (usually a spouse) the larger family and on society is hardly disputed, there is remarkably little solid information about the problem. There are no formal studies that demonstrate the cost-effectiveness of early recognition of the non-motor symptoms that most seriously affect patients’ QoL and by extension that of their carers and associates.

Few studies have addressed even the direct costs of home versus hospital care for PD patients and fewer still have attempted a rigorous estimate of the cost to ‘informal’ carers.

- A UK-based cost analysis estimated direct costs of £4189/year for PD patients managed at home versus £19,338 for full-time institutional care.
- Hagell estimated the cost for PD patients in good health to be one-third that for those in poor health with the greatest health-related differences between the two groups being fatigue, pain, and depression.
- Burn noted a conservative estimate (excluding socio-economic costs such as lost wages of caregivers) by the Parkinson’s Disease Society (UK) putting the annual per-patient cost at £42,000. Estimated direct costs to health and social services were put at £380 million annually.

Models of the overall socio-economic cost of PD must include also the economic value of the burden borne by ‘informal’ caregivers. Reliable data for PD caregivers are rare if not altogether absent. Carers UK quote overall figures:

- There are 3 million working carers in the UK; 45% male, 55% female, providing support that would otherwise cost the tax-payer at least £57 billion per year.
- Three of every five people will become carers at some point in their lives.
- Many will have to give up employment to care.

In one US-based study, ‘informal’ PD caregivers spent 22 hours per week in that role. As 85% of the PD patients involved were in the first 5 years following diagnosis, it is likely that the 22-hour average is quite conservative. However, assuming a modest £15.00/hour rate, this would equate to £17,160/year/patient or £1887 million for the 110,000 PD patients estimated for the UK in 2000.

The major impact of disability for both patients and their ‘informal’ carers is clear from the distribution of costs contributing to the total socio-economic burden of PD. The WHO, based on a report of the use of medical services in the US by a large number of PD patients, have published the distribution of overall cost in five categories.

- Productivity Loss: 49.4%
- Inpatient Care: 19.9%
- Uncompensated (‘informal’) Care: 18.8%
- Outpatient Care: 7.5%
- Prescription Drugs: 4.4%

It is obvious that the cost of disability – to which non-motor symptoms are the major contributors – far outweighs the direct costs of medical care. The need for effective clinical management of non-motor symptoms must be equally apparent.
Both in terms of optimal clinical management of PD and the related socio-economic costs, the burden and importance of non-motor symptoms of PD can hardly be overstated. Fortunately, for patients, their carers and associates, attention is now being directed not only toward amelioration of the primary motor symptoms, but also toward identification and management of the associated non-motor symptoms, which are now clearly recognised as the primary determinants of disability and QoL for both patients and carers.

**Assessment of non-motor symptoms**

Despite their prevalence and dominant effects upon the patient’s disability as well as the QoL of both patients and carers, non-motor symptoms remain often undetected by clinicians and not reported by patients themselves. Shulman reported that depression and other non-motor symptoms of PD were missed by 59% of neurologists. Moreover, only 1% of patients reported depression as a problem whilst 50% qualified as depressed using the Beck Depression Inventory (BDI). Clinically significant non-motor symptoms, including side effects of treatments, are very common and the range of potential symptoms is staggering. Chaudhuri et al. suggested a list of 45 symptoms divided into six categories including:

- Neuropsychiatric symptoms (seven symptoms)
- Sleep disorders (seven symptoms)
- Autonomic symptoms (12 symptoms)
- Gastrointestinal symptoms (overlaps with autonomic symptoms; eight symptoms)
- Sensory symptoms (three symptoms)
- Other symptoms (six symptoms)

Clearly, neither the incidence nor importance of each non-motor symptom is equal, but it has been suggested that every PD patient will suffer from some of these symptoms during their life with the disease. The most prevalent, and arguably the most serious, include affective symptoms, particularly anxiety and depression.

The Global Parkinson’s Disease Survey found that, although the Hoehn and Yahr stage and medication were both significant (p<0.05), that collectively they explained only 17.3% of the variance in Health-Related QoL (HRQL). Coupled with three other significant factors – depression as assessed by the BDI (p<0.001), ‘satisfaction with the explanation of the condition at diagnosis’ (p<0.05), and ‘current feelings of optimism’ (p<0.05), nearly 60% of variability in HRQL was explained. Of these factors, depression was the most important predictor of variability in HRQL.

Consequently, due to their impact and prevalence, depressive symptoms and depression deserve special attention in diagnosis, assessment and management of PD patients.
- Depressive symptoms have been reported in more than half of PD patients
- Depression may precede the motor symptoms of PD
- Due to an overlap of depressive and motor symptoms of PD, NICE recommend that clinicians “…should have a low threshold for diagnosing depression”
- Depressive symptoms may be associated with cognitive impairment, raised homocysteine
Depression can affect the motor state\(^1\)

Increasing severity of depression and worsening cognition are associated with greater disability on activities of daily living, impaired functional ability, psychosis, age, duration of disease, apathy, sleepiness, and motor impairment\(^2\)

The PD patient’s depression significantly degrades the caregiver’s QoL\(^2\)

To date, there is no comprehensive instrument to assess the full range of non-motor symptoms. NICE gives guidance for some of the more common non-motor symptoms\(^4\) and has called for more evidence about better care for non-motor symptoms. A specific screening tool — the Non-motor Symptom Questionnaire (NMSQuest)\(^3\) has recently become available and the Movement Disorder Society (MDS) adaptation of the Unified Parkinson’s Disease Rating Scale (UPDRS) to include assessment of some non-motor symptoms — MDS UPDRS\(^25,26\) is being validated.\(^2\)

The Short Parkinson’s Evaluation Scale (SPES)\(^27\) may provide a validated alternative to the MDS UPDRS, but neither covers important symptoms such as sexual dysfunction, olfaction, apathy, or REM-sleep behavioural disorder (RBD).

There are several scales developed in the SCOPA programme (Scales for Outcomes in Parkinson’s disease) that address not only the classical symptoms of PD (SCOPA-motor),\(^28\) but also non-motor aspects. For other symptoms, conventional scales will have to suffice. Assessments that should be helpful in detecting non-motor symptoms and tracking the outcomes of treatment are outlined below.

**Neuropsychiatric disturbances**

Neuropsychiatric disorders are important determinants of QoL and caregiver burden in PD.\(^9\) More research is needed to establish effective treatments.\(^4\)

**Depression**

As noted, depression is the dominant single symptom degrading QoL in PD patients and their carers

- Clinician-rated:
  - Beck Depression Inventory – BDI (validated in PD)\(^29,30\)
  - Hamilton Depression Rating Scale – HAMD (not specific for PD)\(^31\)

- Patient-rated:
  - Hospital Anxiety Depression Scale – HADS (not specific for PD)\(^32\)

**Anxiety**

Anxiety disorders, including off-period panic attacks and specific phobias, are quite common and are often associated with depression. Prevalence is generally reported around 40%, and up to 63% in a cohort of PD patients with significant sleep disturbances.\(^19\)

- Clinician-rated:
  - Hospital Anxiety Depression Scale – HADS (not specific for PD)

- Patient-rated:
  - Beck Anxiety Inventory\(^33\)
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**Sleep disorders**
Sleep disorders affect nearly all PD patients, appear early in the clinical course of PD, and contribute to excessive daytime sleepiness. All of these symptoms have significant adverse effects on the QoL of both patients and their carers. REM behaviour disorder, in which patients physically enact their dreams, affects one-third of patients, usually precedes the onset of motor symptoms and predicts PD in 40% of cases.34,35

Assessments that can be useful include:
- Parkinson’s Disease Sleep Scale36
- SCOPA-sleep37
- Epworth Sleepiness Scale (not specific for PD)38

**Fatigue**
Fatigue has been reported in nearly 75% of PD patients19 with consequent degradation in functional ability and QoL.

Assessments that can be useful include:
- Fatigue Severity Scale39
- Parkinson Fatigue Scale (PFS-16) – self-report40

**Cognitive impairment**
Estimates of the prevalence of cognitive impairment in PD range from 20% to 93% depending probably on how cognitive impairment is defined and assessed. Overall, including benign forgetfulness Colosimo41 has suggested that 93% of PD patients show some degree of cognitive impairment. Janvin42 in a cohort of 103 PD patients found 27 (26%) met criteria for dementia whilst among the 76 non-demented patients, 42 (55%) had a mild cognitive impairment.

Dementia occurs in up to 40% of patients and is associated with shorter life expectancy.43 Hallucinations (usually visual) often occur in association with cognitive disorders.

Assessments that can be useful include:
- SCOPA-Cog44 – a short, reliable instrument sensitive to the specific cognitive deficits in PD
- Mini-Mental State Examination (MMSE)45

Although commonly used to screen for cognitive decline, the MMSE has not been specifically validated in PD and parts requiring a degree of motor skill should probably be discounted.

**Autonomic dysfunction**
The prevalence of orthostatic dizziness, constipation, bladder dysfunction, erectile dysfunction, and hyperhidrosis is significantly higher among PD patients than matched controls.24 Half of PD patients rated their effect on daily living as ‘a lot’ or ‘very much’.46 Orthostatic hypotension and dizziness are associated with an increased risk of falls and resulting fractures.
Potentially useful assessments of autonomic dysfunction include:

- SCOPA-Aut – a questionnaire to evaluate autonomic dysfunction in PD
- QSART – quantitative sudomotor axon reflex test for sudomotor function
- Urodynamic studies – uroflowmetry and cystometry (bladder dysfunction)
- Defaecating proctography (bowel dysfunction)
- Postural hypotension – 60 degrees head-up tilt test with cardiovascular monitoring
- Sympathetic skin response
- Pupil function tests with pilocarpine or phenylephrine

**Impulse control disorders**

Several complications apparently related to high-dose dopaminergic treatments for PD are comparatively infrequent, but deserve attention because they are socially disabling when they occur.

Punding involves compulsive, stereotypical, repetitive, and purposeless behaviours that are similar, but distinct from obsessive-compulsive disorder. In a series of 50 patients with higher dopamine replacement therapy (>800 levodopa [L-dopa] equivalent units/day), from 123 unselected PD patients Evans et al identified 17 (14%) patients with punding.

Management of punding involves reduction of dopaminergic doses. In a report of three cases Meseguer reported improvement in all with reduction of dopaminergic doses.

There is neither any specific scale or screening instrument to assess punding nor common diagnostic criteria. Clinicians will need to rely upon interviews as patients with punding appear to be aware of their behaviour but information from carers may be most helpful.

Pathological gambling is one of the impulse control disorders that can have disastrous consequences and is related to dopaminergic agonists. In a series of 297 PD patients and using rigorous criteria for impulse control disorders (ICDs), Voon et al found lifetime prevalence of 3% for pathological gambling, 2.4% for pathologic hypersexuality and 0.7% for compulsive shopping, giving lifetime prevalence of the three ICDs of 7.1%, which increased to 13.7% in patients on dopamine agonists.

In another series involving 272 PD patients, Weintraub et al found 6.6% met criteria for an ICD at some point during the course of PD. A multivariate model showed that treatment with a dopamine agonist (p=0.01) and a history of ICD symptoms prior to PD onset (p=0.02) predicted current ICD. There were no differences between the dopamine agonists in their association with ICDs (p=0.21) and daily doses of dopamine agonists were higher in patients with an ICD than in those without an ICD (p<0.001).

In the Weintraub series, the presence of compulsive gambling, buying, or sexual behaviour was assessed using the Minnesota Impulsive Disorders Interview.

Clearly, assessment and treatment (see below) of non-motor symptoms are intended to avoid deterioration and to improve QoL and disability. Therefore, QoL and disability should be assessed in conjunction with the non-motor symptoms of PD, as these symptoms have the greatest impact on QoL and disability.
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QoL
PDQ 39 – the Parkinson’s Disease Questionnaire 39 – is a disease specific instrument including eight domains:\(^{53,54}\)
- Mobility
- Activities of daily living
- Emotional well-being
- Stigma
- Social support
- Cognition
- Communication
- Bodily discomfort

Disability
WHO DAS II\(^{55}\) – the World Health Organization Short Disability Assessment Schedule – is a disease-independent evaluation of disability in six domains:
- Understanding and communicating
- Getting around
- Self care
- Getting along with people
- Life activities
- Participation in society

The WHO-DAS is available in interview, self-administered, and proxy self-administered versions both long (36 item) and short (12 or 6 item) from the WHO website. It has been widely used in patients with a variety of diagnoses.

Treatment of non-motor symptoms
There is an association between the severity of motor symptoms and the incidence of non-motor symptoms, but the relationship is weak and non-motor symptoms are characteristically unresponsive to L-dopa.\(^{56}\) In a long-term follow up study, Hely et al\(^{56}\) found an elevated standardised mortality rate of 1.86. Among the one-third of the original cohort surviving 15 years after diagnosis of PD:
- 81% suffered falls; 25% had fractures
- 84% showed cognitive decline
- 48% met criteria for dementia
- 50% had hallucinations
- 50% were depressed
- 50% had choking episodes
- 50% had symptomatic postural hypotension
- 35% suffered urinary incontinence
- 40% were in care facilities
- 95% had suffered from L-dopa-induced dyskinesias/dystonias, but in most cases these were not disabling
They concluded “Neuroprotective interventions in Parkinson’s disease should be judged by their ability to improve non-L-dopa-responsive aspects of the disease, rather than just by their capacity to delay the introduction of L-dopa or reduce its associated side effects”.

Because non-motor symptoms are generally unresponsive to dopaminergic drugs, clinical management will require interventions commonly used to treat the emergent symptom, but keeping in mind that PD patients are often elderly, at risk for drug–drug interactions and often require doses differing from those for healthy adults. Some possible pharmaceutical interventions have been suggested by Chaudhuri et al, Table 2.57

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<thead>
<tr>
<th>Neuropsychiatric Symptoms</th>
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<tbody>
<tr>
<td>Depression</td>
<td>SSRIs, reboxetine, pramipexole</td>
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<tr>
<td>Apathy, anhedonia</td>
<td>modafinil, pramipexole, testosterone</td>
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<tr>
<td>Fatigue</td>
<td>modafinil, testosterone replacement</td>
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<tr>
<td>Dementia</td>
<td>cholinesterase inhibitors (rivastigmine), memantine, oestrogen</td>
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<tr>
<td>Hallucinations</td>
<td>Atypical antipsychotics (clozapine,quetiapine)</td>
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<thead>
<tr>
<th>Sleep Disorders</th>
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<tbody>
<tr>
<td>REM behaviour disorder</td>
<td>clonazepam, pramipexole, melatonin</td>
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<tr>
<td>Restless legs</td>
<td>gabapentin, apomorphine, dopamine agonists (ropinirole)</td>
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<tr>
<td>Periodic limb movements</td>
<td>dopamine agonists</td>
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<tr>
<td>Excessive daytime sleepiness</td>
<td>modafinil</td>
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<tr>
<th>Autonomic Symptoms</th>
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<tr>
<td>Bladder disturbances</td>
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<tr>
<td>Orthostatic hypotension</td>
<td>fludrocortisone, ephedrine, milodrine</td>
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<tr>
<td>Sexual dysfunction</td>
<td>PDE5 inhibitors (sildenafil), testosterone replacement</td>
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<th>Gastrointestinal Symptoms</th>
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<th>Sensory symptoms</th>
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<tr>
<td>Pain</td>
<td>gabapentin</td>
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Table 2. Summary of conventional and newer strategies for treatment of some non-motor symptoms. (Adapted from Chaudhuri et al. Reproduced with permission of tbc)

Note to MB & JR: attempts to obtain permission to use this figure are ongoing – Professor Chaudhuri has confirmed that the table is not in his 2006 Lancet Neurology publication and I have asked him to confirm if the table has been published elsewhere.
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Summary and conclusions
There is compelling evidence that non-motor symptoms of PD play a dominant role in the QoL and disability of PD patients and the QoL of their ‘informal’ carers. Effective clinical management of PD therefore demands that these symptoms be identified and, to the extent possible, treated. Dopaminergic drugs are largely ineffective against the most common and debilitating non-motor symptoms.

It seems unreasonable to expect that a single clinician will or should possess the range of expertise required to diagnose and manage both motor and the range of non-motor symptoms prevalent in PD. A team approach will be needed involving clinicians and other medical staff collectively to bring a range of expertise and skills to bear on the overall management of PD.

References
34. Schenck CH, Bundle SR, Mathowal MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder. Neurology 1996;46:388–393
41. Colosimo C. Cognitive and behavioural problems in Parkinson’s disease. Presentation at the European Parkinson’s Disease Association meeting 2006
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55. World Health Organization Classification, Assessment, and Survey Team. WHO-DAS II: Disability Assessment Schedule. WHO 2000

Chaudhuri ref: Please see note on page 84