Therapeutic strategies in Parkinson’s disease (PD) provide control of motor (nigral) and nonmotor (extranigral) symptoms. Nigral dopamine-related signs and symptoms are addressed by supplementation or substitution of cerebral dopamine, and extranigral nondopamine-related symptoms are treated by addressing specific autonomic, neuropsychiatric and sleep dysfunctions. However, the ultimate goal in treating PD is to slow, stop or modify disease progression through early and appropriate intervention. Recognition of the various nonmotor clinical manifestations of PD is critical to early diagnosis and treatment. Disease-modifying drugs, once identified, should be initiated as soon as possible, preferably in the prodromal (premotor) phase of the disease. In this review, clinical signs and symptoms of this phase will be described, as will the (suggested) criteria for diagnosis and optimal initiation of disease-modifying agents. Both symptomatic and disease-modifying agents applicable in the premotor phase of PD will also be addressed.

**Keywords:** autonomic dysfunction • disease-modifying agents • neuropsychiatric symptoms • Parkinson’s disease • Parkinson’s disease diagnosis • premotor symptoms • prodrome • REM sleep behavior disorder

The premotor phase of Parkinson’s disease

Parkinson’s disease (PD) is a neurodegenerative disorder characteristically manifesting with the clinical hallmarks of motor parkinsonism, bradykinesia, hypokinesia or akinesia, rigidity, tremor, and postural instability, caused by significant nigral degeneration-derived dopaminergic striatal denervation. The classic diagnostic criteria include only clinical signs of motor parkinsonism. In the past decade it has become increasingly accepted that in PD nonmotor signs and symptoms may accompany motor parkinsonism, and that there is substantial clinical variability among patients. The nonmotor manifestations of PD include autonomic (i.e., gastrointestinal dysfunction, urinary and sexual dysfunction, orthostatic hypotension, and hyperhidrosis), sleep (i.e., impaired sleep initiation and maintenance, rapid eye movement [REM] sleep behavior disorder [RBD] and excessive daytime sleepiness), sensory (i.e., pain, hyposmia and visual dysfunction) and/or neuropsychiatric (i.e., depression, anxiety and panic attacks, dementia, and psychosis) disturbances that cannot be explained by the nigral dopaminergic pathology of PD. As the occurrence of these extranigral nonmotor symptoms is increasingly recognized to precede the first motor manifestations of PD by many years in some patients, the existence of a so-called ‘premotor’ or ‘prodromal’ phase [1–3], whether symptomatic or asymptomatic, has been proposed and debated [4]. Although data regarding the existence of a premotor phase are inconsistent, the convergence of the strongest evidence (i.e., from prospective studies) supports the existence of a prodrome. The onset of the premotor phase and the sequence of prodromal symptom manifestations relative to the emergence of motor symptoms and of basal ganglia changes have yet to be established [2].

Before examining this nonmotor phase in detail, a synopsis of the most convincing evidence from pathological examinations will be presented.

**Pathological evidence of a premotor phase**

The premotor phase of PD is strongly supported by Braak’s recent observations of Lewy bodies and Lewy neuritis with α-synuclein immunostaining [1]. According to Braak, synucleinopathic lesions begin to develop in PD a considerable
amount of time prior to the appearance of motor dysfunction. Braak’s classification divides pathological synucleinopathy in PD into six chronologically distinct stages. Based on this classification, synucleinopathic involvement of the structures suggested to underlie motor parkinsonism – the substantia nigra (SN), tegmental pedunculopontine nucleus, oral raphe, amygdala, magnocellular nuclei of the basal forebrain and tuberomammillary bodies – does not become evident until stage 3. This stage straddles the premotor and motor phases of PD. In the earlier Braak stage 1, there is α-synuclein immunoreactivity in the anterior olfactory structures, as well as PD-related inclusion bodies within the spindle-shaped projection neurons of only the dorsal IX/X motor nucleus and the intermediate reticular zone. Here, Lewy neuritis followed by conspicuous Lewy bodies will appear before stage 2; the same findings are seen in the projection neurons of the caudal raphe nuclei, the gigantocellular reticular nucleus and the coeruleus–subcoeruleus complex. In these two stages, however, the SN is still not involved. These two stages represent the premotor phase of PD, as in some patients during these stages nonmotor, but not motor, symptoms may reflect the extent of synucleinopathic degeneration [4], including mainly hyposmia [5–7] and autonomic dysfunctions [8].

**Clinical features of the premotor phase**

The premotor phase of PD may or may not be associated with discomfort due to autonomic dysfunction, sleep disturbances, sensory dysfunctions, neuropsychiatric disorders or other less frequently documented symptoms, such as restless legs and fatigue [4].

**Autonomic dysfunction**

Symptoms of dysautonomia in PD are well known nonmotor features [9–13]. These symptoms include constipation, orthostatic hypotension, urogenital disturbances, salivary sweating, excessive sweating and temperature dysregulation. There is evidence that many of these autonomic disturbances emerge during the premotor phase of PD.

**Constipation**

Several studies have shown that constipation and/or a delay in colonic transit can precede PD motor symptoms by many years [9,10,14–16]. As part of the Honolulu Heart Program study, men who reported having less than one daily bowel movement had a risk of developing PD 2.7-times higher than that of men who had daily bowel movements, and four-times higher than that of men who had two or more bowel movements each day (after adjustment for age, pack-years of cigarette smoking, coffee consumption, laxative use, jogging, and the intake of fruits, vegetables and grains) [9]. In patients with less than one daily bowel movement, constipation can be explained by Lewy bodies and α-synuclein deposits in the dorsal vagus nucleus and enteric plexus preceding the involvement of the SN [1,17,18]. Other, more severe, complications, such as megacolon, volvulus and bowel occlusion, are less common during the premotor phase and are mostly reported late in the disease [19,20]. The results of this study are noteworthy particularly given the use of prospective assessment methods, which are not influenced by selective recall bias. Although a detailed discussion is beyond the scope of this review, it should also be noted that midlife obesity has been suggested to be associated with the development of PD [21], although this putative association remains controversial [22]. In another prospective study, patients with PD were shown to have greater all-cause mortality after adjustment for smoking, age and disease-related characteristics [23]. Studies have confirmed the observation that caffeine consumption and cigarette smoking appear to have some protective effects against the development of PD [24], although the clinical significance of these findings is far from clear.

**Orthostatic hypotension**

Orthostatic hypotension in PD patients is usually considered an adverse effect of dopaminergic treatment that typically develops later in the disease process. Orthostatic hypotension is defined as a fall in systolic pressure of at least 20 mmHg and in diastolic pressure of at least 10 mmHg, between lying supine for 15 min and then standing for 5 min. If blood pressure problems emerge earlier and are prominent, the diagnosis of multiple system atrophy (MSA) is often considered [25]. Although uncommon, orthostatic hypotension may also occur early in the disease or may precede or overshadow motor parkinsonism [26].

**Urogenital disturbances**

Bladder disturbances are common in patients with PD and typically take the form of complaints of frequency, urgency and/or urge incontinence, although dysuria and urinary retention have also been reported [27]. A recent report of a patient with long-standing orthostatic hypotension and urinary disorders that emerged before being diagnosed with PD suggests that urinary disturbances may occasionally precede motor parkinsonism [28]. In the differential diagnosis of PD and MSA, large postvoid residuals, open bladder neck and neurogenic change in sphincter motor unit potentials are rather common in MSA, but not PD; patients suffering PD with dementia or dementia with Lewy bodies, however, may also typically show large postvoid residuals and neurogenic change in the sphincter motor unit potentials, mimicking MSA [29].

Sexual dysfunction occurs in many PD patients and can be the consequence of both PD-related autonomic dysfunction and age-related testosterone deficiency [30]. Erectile dysfunction is also frequent in PD patients. In the general population, erectile dysfunction can be a risk factor for developing PD (associated with a 3.8-times higher risk) but it may also be part of the prodrome, antedating motor parkinsonism by many years [31].

**Sleep disorders**

Sleep dysfunction in PD patients is mainly considered to be the consequence of dopamine deficiency-related akinesia and, therefore, as a rule, correlates with disease severity, PD medication and depression [32]. In the premotor stage, RBD is the main cause of sleeping problems. This parasomnia is suggested to be caused by the pedunculopontine nucleus, responsible for both control of locomotion and REM sleep. RBD is characterized by vigorous movements and increased muscle activity during REM sleep, which may precede motor parkinsonism [33–36]. In a recent follow-up study, 14 out of 93 RBD patients developed PD, seven developed dementia with Lewy bodies, four dementia and one MSA [36]. Another
study reported that 11 out of 29 (38%) patients were diagnosed to have PD at a mean interval of 3.7 ± 1.4 (standard deviation) years after the diagnosis of RBD, and 12.7 ± 7.3 years after the onset of RBD [37]. RBD patients who later developed PD had an elevated REM sleep percentage as well as more periodic limb movements during non-REM sleep [38]. The risk of developing a neurodegenerative disorder is therefore substantial in patients with RBD. Nuclear imaging studies in RBD patients are compatible with subtle (subclinical) striatal dopaminergic denervation, not rising to the level of a PD diagnosis [37,39,40]. For instance, in a patient with a 20-year history of RBD without parkinsonism at autopsy, incidental Lewy bodies were found in the SN and locus coeruleus [41].

Excessive daytime sleepiness can also occur early in PD or predate the diagnosis [42]. The Honolulu–Asia Aging Study showed a more than threefold excess in the risk of PD in patients with excessive daytime sleepiness [43]. As the coeruleus–subcoeruleus complex, lower raphe and pedunculopontine nucleus are involved in Braak stage 2–3, these sleep symptoms may well predate the motor symptoms [44].

Sensory dysfunction
There is a wide spectrum of sensory disorders in PD patients, but only hyposmia and pain are characteristic sensory features of the premotor phase. The majority of PD patients suffer olfactory disturbances, which might be recognized even in drug-naive patients. Most studies find no relationship between disease severity and the degree of olfactory dysfunction, as measured by odor detection or identification, although one report suggests such an association using a measure of odor discrimination [45–47]. It is possible that the early development of this olfactory disorder may peak before the emergence of progressive motor symptoms [48]. In a case–control study, 68% of PD patients reported hyposmia at the onset of their motor symptoms, compared with 3% of controls [49]. As part of the Honolulu–Asia Aging Study, olfaction was assessed from 1991 to 1996 in 2267 men not suffering from motor parkinsonism or dementia at the time of testing. During the 8-year follow-up period, 35% of them were diagnosed with PD; the average time to diagnosis was 4.0 ± 1.9 (range: 1–8) years. During the first 4 years of follow-up, the odds ratio for PD was 5.2 in men within the lower quartile for olfactory function compared with those in the two top quartiles [50]. In another well-designed prospective study, four out of 40 hyposmic, non-parkinsonian relatives of PD patients, but none of the 38 other (normosmic) relatives, showed decreased [123I] β-carbomethoxy-3β-(4-iodophenyltropane) (CIT) binding ratios on single photon-emission computed tomography (SPECT) at baseline and were clinically diagnosed with PD within 2 years. Furthermore, the mean decline of β-CIT binding in all relatives who underwent a second scan after 2 years as part of this study was significantly greater in the hyposmic than in the normosmic relatives [51]. In a prospective World War II veteran twin study, 19 twins completed all study evaluations; from that group, two twins developed PD. Although neither twin suffered impaired smell identification at baseline, the average decline in olfactory function in these twins was greater than in the 17 twin pairs who did not develop PD [52]. These studies provide strong evidence that in PD impaired olfactory function typically occurs before motor parkinsonism [50].

In 15% of the PD patients participating in a study of the Queen Square Brain Bank for Neurological Diseases, pain was reported as the presenting symptom in PD. In this study, a retrospective analysis of 309 consecutive PD patients revealed that 35 (11%) patients suffered shoulder pain preceding the onset of motor symptoms by several years, correlating retrospectively with the side of maximum severity of motor parkinsonism. In seven (20%) patients, shoulder pain was the presenting complaint [53]. In PD patients, α-synuclein was found in the spinal cord lamina I neurons, which are thought to be involved in the pain pathway [54]. This might explain premotor pain; later in the disease, the nature of the pain might be rather multifactorial, caused by a number of comorbid conditions, such as (fluctuating) rigidity and dystonia.

Neuropsychiatric disorders
Apathy, anxiety, panic attacks and depression are additional non-motor problems in PD, not only during the motor but also during the premotor phase. The prevalence of these conditions in PD patients is estimated to be 2–3-times higher than in the general elderly population. The reason for this increased frequency is not well understood, but synucleinopathy degeneration of the noradrenergic, serotonergic and cholinergic brainstem centers (preceding nigral involvement) and psychosocial factors may play a role. Prevalence rates of depressive disorders in PD vary widely, but a recent meta-analysis of published studies revealed a weighted prevalence rate of 17% for major depression, 22% for minor depression and 13% for dysthymia [49]. Using structured interviews to establish Diagnostic and Statistical Manual (DSM)-III criteria, the reported prevalence of major depressive disorder was 19%, while in studies using DSM criteria without a structured interview, the reported prevalence of major depressive disorder was only 7%. Depression was the presenting symptom in 2.5% of 433 pathological proven PD cases at the Queen Square Brain Bank for Neurological Diseases [56]. In particular, anxiety-driven depressive episodes have been found to predate motor symptoms by several years [57].

Diagnosis of PD during the premotor phase
The data reviewed here may point to an earlier onset of PD than is suggested by the occurrence of the motor symptoms currently used in the clinical diagnosis of PD. This assumption is mainly supported by Braak’s proposal that PD-related synucleinopathy pathology spreads through a caudal–rostral pattern with involvement of the (para)sympathetic nervous system, olfactory and lower bulbar structures long before the SN is involved in Braak stage 3. As a result of this premotor synucleinopathy involvement before motor parkinsonism becomes overt, PD may manifest with hyposmia, constipation and urogenital symptoms, as well as neuropsychiatric symptoms [44]. When the process moves upwards to the basal portion of the midbrain, RBD may express the stage 3 involvement of the pedunculopontine nucleus before nigral degeneration reaches the clinical threshold (suggested to take ~5–6 years). This may explain the relatively short duration of this disorder prior to the appearance of motor symptoms. The nonspecific nature of the previously mentioned symptoms, however, normally does not permit presumptive diagnosis without other supporting features.
As disease-modifying treatments become available, early (premotor) diagnosis is an imperative goal in order to reach optimal effects of this treatment. Undoubtedly, the technology to identify individuals with early nonmotor features of PD, subclinical impairments in dopamine metabolism and/or relevant genetic factors is available.

**Identification of (subclinical) idiopathic PD with brain imaging**

MRI of the CNS offers some differential diagnostic potential in differentiating PD from MSA, progressive supranuclear palsy (PSP) and/or corticobasal degeneration (CBDG) and vascular Parkinsonism, but is not very helpful in the detection of early (premotor) PD. Although signal void in the SN has been reported, this has not emerged as a sensitive marker.

As for functional neuroimaging, PET scans in PD patients show characteristic asymmetrical reduced putaminal uptake of the presynaptic dopaminergic ligand fluorine-18-labeled-levodopa (18F-dopa), and reductions in putaminal K_v-values of 18F-dopa uptake correlated with disease duration and severity. In some asymptomatic first-degree PD relatives, 18F-dopa PET scans enable identification of preclinical PD-related nigrostriatal dysfunction. As is the case in dopamine transporter (DaT)-SPECT, however, nearly 10% of all early PD patients have a normal uptake of radioactivity, suggested to be the result of the compensatory upregulation of the aromatic amino acid decarboxylase enzyme in preserved dopaminergic terminals.

Recently, two presynaptic dopaminergic terminal SPECT ligands, β-CIT and fluoropropyl (FP)-CIT (DaT) have become available for clinical practice. In PD, even in the premotor stages, asymmetrical reduction in striatal DaT binding can be established. As DaT-SPECT offers a sensitive tool to provide a quantitative biomarker to record PD-related progressive nigrostriatal dopaminergic degeneration and also enables differential diagnosis of PD from nonparkinsonian tremors, drug-induced Parkinsonism, psychogenic Parkinsonism and vascular Parkinsonism, it has been proposed as a reliable tool in the diagnosis and evaluation of PD. However, its usefulness is limited by both the fact that in 10% of early PD patients DaT-SPECT binding is found within normal limits and that there are difficulties in the differentiation of PD with MSA, PSP and CBDG.

Recent studies have also shown that the 123I-labeled metaiodobenzylguanidine SPECT ligand, β-CIT and fluoropropyl (FP)-CIT (DaT) have become available for clinical practice. In PD, even in the premotor stages, asymmetrical reduction in striatal DaT binding can be established. As DaT-SPECT offers a sensitive tool to provide a quantitative biomarker to record PD-related progressive nigrostriatal dopaminergic degeneration and also enables differential diagnosis of PD from nonparkinsonian tremors, drug-induced Parkinsonism, psychogenic Parkinsonism and vascular Parkinsonism, it has been proposed as a reliable tool in the diagnosis and evaluation of PD. However, its usefulness is limited by both the fact that in 10% of early PD patients DaT-SPECT binding is found within normal limits and that there are difficulties in the differentiation of PD with MSA, PSP and CBDG.

Since the initial report by Becker on transcranial sonography (TCS), several independent studies have reported hyperechogenicity of the SN in up to 90% of patients with PD. However, SN hyperechogenicity is also seen in CBDG and dementia with Lewy bodies. Although SN hyperechogenicity is not associated with disease severity and progression, SN size has been found to correlate with young age at PD onset. In retrospective studies, the use of TCS in PD patients, in later stages, has enabled the differentiation of idiopathic PD from MSA and PSP, with high sensitivity and specificity. In a recent prospective blinded study, 60 early-stage PD patients were studied with TCS at baseline and followed up for 1 year, whereas raclopride PET, or DaT-SPECT or both were performed in patients with persistent diagnostic uncertainty. TCS-sensitivity at baseline was 90.7%, and specificity was 82.4%; the positive predictive value of TCS for PD was 92.9%.

**Identification of (subclinical) genetic PD**

To date 13 genetic loci have been associated with autosomal dominant and recessive PD. Defects or dysfunction of certain genes, such as α-synuclein gene (PARK1), parkin gene (PARK2), ubiquitin carboxyl-terminal hydrolase (UCHL-1) gene (PARK5), PINK1/PARK6, DJ-1 (PARK7), LRRK2 (PARK8) and Nurr1, have been reported to be linked with familial PD. Four of the PARK genes, SNCA at PARK1, UCHL-1 at PARK5, PARK6 and LRRK2 at PARK8, have been implicated in sporadic PD. Of these, only tests for the parkin gene are commercially available. Tests for other genes are only available at specific research centers.

**Premotor diagnosis of PD**

Premotor diagnosis in PD is still an enigma, although it needs to be established. Siderowf and Stern proposed a ‘PD at-risk syndrome’ with a hierarchical taxonomy with four distinct levels: prephysiologic, preclinical, premotor and prediagnostic preceding PD. Further to these, we propose new criteria for diagnosing this disorder that enables clinicians to treat those patients with emerging disease-modifying antiparkinsonian agents. In our opinion, in case of unexplained hyposmia or another potentially PD-related nonmotor symptom (e.g., constipation, urogenital problems and pupillomotor abnormalities) and sympathetic (drenching sweats) cholinergic disorders, as well as sympathetic adrenergic disorders (i.e., cardiovascular dysfunction, baroreflex failure and/or orthostatic hypotension), PD-related neuropsychiatric disorders may manifest as otherwise unexplained apathy, anxiety and panic attacks, mild cognitive impairment, dementia and/or...
Hughes signs of motor parkinsonism. Based on positive genetic testing in combination with one of the nonmotor symptoms. Genetic PD diagnosis is set by characteristically post-mortem findings with a history of motor parkinsonism. Definitive diagnosis of PD, however, is only set by characteristically post-mortem findings with a history of motor parkinsonism and/or PD-related nonmotor symptoms. Genetic PD diagnosis is based on positive genetic testing in combination with one of the signs of motor parkinsonism.

Cases with probable diagnosis might be considered clinically definite PD when there is unequivocal response to levodopa. Definitive diagnosis of PD, however, is only set by characteristically post-mortem findings with a history of motor parkinsonism and/or PD-related nonmotor symptoms. Genetic PD diagnosis is based on positive genetic testing in combination with one of the signs of motor parkinsonism.

Of course, the previous PD exclusion criteria as described by Hughes et al. will have to be modified [88], as early premotor autonomic disorders and/or dementia might serve as PD-related nonmotor signs, heralding motor parkinsonism in PD (Box 1).

### Treatment of premotor PD

To date, available therapeutic strategies in PD provide symptomatic control of motor (nigral) and nonmotor (extranigral) symptoms. Nigral dopamine deficiency-related signs and symptoms are mainly addressed by supplementation or substitution of cerebral dopamine. These symptoms will not be discussed, as by definition they become overt only after the PD premotor phase.

The ultimate goal in the treatment of PD, however, is not to control the symptoms, but rather to slow, stop or modify the progression of the disease as soon as possible with disease-modifying drugs. Here, both symptomatic and disease-modifying agents applicable in the premotor phase of PD will be discussed in detail.

#### Symptomatic agents

**Constipation**

Basic treatment of constipation in PD includes recommendation of a high fiber diet, psyllium preparations, adequate hydration and exercise. When this is not adequate, domperidone, a dopamine antagonist that does not cross the BBB, can also be used. The prostaglandin misoprostol, at a dosage of 400 µg/day, has been shown to shorten colonic transit time and to increase the number of bowel movements per week in patients with severe idiopathic constipation [89]. Other anticonstipation agents that are of proven efficacy are osmotic laxatives such as polyethylene glycol (17 g/day) or lactulose (10–40 g/day).

**Urogenital problems**

The treatment for neurogenic detrusor overactivity dysfunction should be based on individual patient evaluation, including urodynamic investigation of voiding dysfunction. Treatment options include antimuscarinic drugs, such as extended release oxybutynin chloride (20 mg/day), long-acting tolterodine (2–4 mg/day) and/or darifenacin (7.5–15 mg/day), which, due to its selective M3 agonistic action, is less apt to block central M1 receptors [92]. By inhibiting the binding of acetylcholine to muscarinic receptors in the detrusor muscle, involuntary bladder contractions will be prohibited.

In elderly patients, ionic trospium (20 mg at bedtime or twice daily), which does not penetrate the CNS, might be preferred. Recently, solifenacine (5–10 mg once a day) has been approved for the treatment of an overactive bladder [90]. Another option in case of a refractory overactive bladder is offered by botulinum toxin injections into the bladder wall [91]. In case of an areflexic detrusor and high postvoid residual urine volumes, intermittent catheterization is advised [92].

Phosphodiesterase type 5 inhibitors are considered to be the first-line therapy for the treatment of erectile dysfunction. There are no compelling data to support the superiority of one phosphodiesterase type 5 inhibitor over another [93]. The patient should be started on a middle dose of chosen medication (50 mg of sildenafil, 10 mg of tadalafil or 10 mg of vardenafil). Best results, however, are obtained by the stimulation of endogenous nitric oxide with psychic (fantasy) and physical (penile) stimulation. Medications should not be used more than once per 24 h.

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**Table 1. Suggested diagnostic criteria for possible, probable and definite idiopathic and/or genetic PD.**

<table>
<thead>
<tr>
<th>PD type</th>
<th>Positive test</th>
<th>Symptoms not otherwise explained</th>
</tr>
</thead>
</table>
| Clinically possible PD | Fluorodopa PET and/or DaT SPECT in combination with MIBG SPECT or TCS | Nonmotor: Hyposmia or RBD and/or AD or neuropsychiatric disorder  
Motor: Bradykinesia, muscular rigidity or 4–6 Hz rest tremor |
| Clinically probable PD | Fluorodopa PET or DaT SPECT | Nonmotor: Hyposmia in combination with RBD and/or AD or neuropsychiatric disorder  
Motor: Bradykinesia in combination with muscular rigidity or 4–6 Hz rest tremor |
| Genetic PD       | Genetic test                                                                 | Nonmotor: Definite response to levodopa  
Motor: Bradykinesia, muscular rigidity or 4–6 Hz rest tremor |
| Clinically definite PD | Clinically probable PD with definite response to levodopa | Nonmotor: Autopsy-proven PD  
Motor: Documented history of levodopa-responsive PD-related motor and nonmotor symptoms |

**AD = parasympathetic (constipation, urogenital problems, pupillomotor abnormalities) and sympathetic (drenching sweating) cholinergic and/or sympathetic (cardiovascular dysfunction, baroreflex failure and/or orthostatic hypotension) dysfunction; neuropsychiatric disorders = apathy, anxiety and panic attacks, mild cognitive impairment, dementia and/or psychosis.**

**AD = parasympathetic (constipation, urogenital problems, pupillomotor abnormalities) and sympathetic (drenching sweating) cholinergic and/or sympathetic (cardiovascular dysfunction, baroreflex failure and/or orthostatic hypotension) dysfunction; neuropsychiatric disorders = apathy, anxiety and panic attacks, mild cognitive impairment, dementia and/or psychosis.**

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REM sleep behavior disorder

Rapid eye movement sleep behavior disorder is considered to be the consequence of cholinergic denervation in its ascending cholinergic pathways to the thalamus [94]. In 90% of the patients, clonazepam (0.5–2 mg before bedtime) has been found to improve RBD mesolimbic structures [95]. Its affinity to the dopamine D3 receptors, mainly localized in the nigrostriatal regions, also restores REM sleep muscle atonia [96]. In 90% of the patients, clonazepam, this drug also restores REM sleep muscle atonia [97]. None of the dopaminomimetics is ineffective in several studies [98]. In 90% of the patients, clonazepam, this drug also restores REM sleep muscle atonia [99]. Donepezil, gabapentin, pramipexole and levodopa also have been reported to be effective.

Pain

Premotor pain is difficult to treat, as its exact mechanism is still unknown. The putative role of the basal ganglia in the modulation of sensory information is reinforced by the antalgic effects of dopaminomimetics.

Hyposmia

There is no treatment for hyposmia unless it reflects an underlying defect or disease of the nose or related organs.

Depression

Despite the high prevalence of PD-related depression, it is still under-reported and undertreated. There is still a marked paucity of controlled studies to evaluate the effects of antidepressants [96]. Citalopram and sertraline, but not amitriptyline, were reportedly ineffective in several studies [97,98]. Although not really established in clinical trials, in daily practice, selective serotonin-reuptake inhibitors are the most popular first-line class of antidepressants prescribed in PD patients [99]. Levodopa and dopamine agonists, such as pramipexole, are also suggested to be effective in the treatment of PD-related depression. This idea is mainly based on the fact that subthalamic deep brain stimulation might control mood [100] and might induce depression, owing to the withdrawal of dopaminomimetics [101]. The effects of pramipexole might be explained by its affinity to the dopamine D3 receptors, mainly localized in the mesolimbic structures [102–104].

Disease-modifying agents

Disease-modifying drugs targeting PD have to target the precise pathogenic mechanisms responsible for cell death in this disease, which are currently not fully known. Of course, it seems justified to assume that these mechanisms include oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammation, proteolytic stress (caused by the excess production of or impaired clearance of misfolded proteins) or other processes involved in the cascade leading to necrosis and/or apoptosis. Indeed, agents interfering with these mechanisms induce some neuroprotection in animal or in vitro models [105–109]. However, consequent studies with these agents in PD patients have, as yet, mostly failed to slow, stop or modify clinical progression [110–112]. To date, no intervention whatsoever (e.g., levodopa, dopamine agonists, selegiline, tocopherol, coenzyme Q, riluzole, immunophilin and glial cell derived neurotrophic factor) has been established to have generally accepted disease-modifying effects and/or neuroprotective effects in PD patients, although initially, owing to confounding symptomatic and/or pharmacological effects of the applied intervention, disease-modifying effects were erroneously suggested [113]. Maybe this failure to develop protective, modifying agents is also the result of the fact that animal and/or in vitro PD models are not relevant to PD, as the applied toxins inducing cell death might not be very relevant to the cause and/or pathogenesis of this disease (for review see [114]).

To counteract these problems, a new clinical (delayed start) design has been promoted, that will theoretically be more successful in discriminating between symptomatic and neuroprotective effects [115]. In this design, drug-naïve PD patients are randomly assigned to initiate and continue therapy, either the study drug or placebo, during enough time to normally establish clinical disease progression. In the second phase, both groups of patients are

<table>
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<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Availability</th>
<th>Cost</th>
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<tbody>
<tr>
<td>Neuropsychologic testing</td>
<td>+</td>
<td>-</td>
<td>Broad</td>
<td>Moderate</td>
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<tr>
<td>Transcranial ultrasound sonography</td>
<td>+/+</td>
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<tr>
<td>Cardiac MIBG imaging</td>
<td>++</td>
<td>++</td>
<td>Broad</td>
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<tr>
<td>Dopamine transporter SPECT</td>
<td>++</td>
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<td>Broad</td>
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<tr>
<td>18F-fluorodopa PET</td>
<td>++</td>
<td>++</td>
<td>Restricted</td>
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<tr>
<td>Genetic testing</td>
<td>++</td>
<td>++</td>
<td>Restricted</td>
<td>High</td>
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</tbody>
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- - Not useful; +: Somewhat useful; ++: Sufficiently accurate to be useful.

MIBG: Metaiodobenzylguanidine; SPECT: Single photon-emission computed tomography.

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treated for the same period with the study drug. In the case that there is a symptomatic effect of the study drug, the difference in clinical progression of disease during treatment with this drug compared with placebo after the first stage will disappear as soon as the placebo-treated group is treated with the study drug (in the second phase). However, if this difference between groups after the first phase persists during the second phase (when both groups are treated with the study drug), this might be explained as a disease-modifying effect.

The first drug studied with this procedure in PD patients was rasagiline. This drug, when tested in a delayed start design in both the Rasagiline TVP-1012 in the Early Monotherapy for Parkinson's disease Outpatients (TEMPO) [113] and Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) [114] studies, showed that the difference in disease progression between comparable early, drug-naive, PD patient groups during double-blind, placebo-controlled treatment in the first phase persisted when both groups were treated with this monoamine oxidase inhibitor in the second phase. Although this points to a disease-modifying effect of this drug, other explanations of this effect now have to be excluded. Theoretically, for instance, this effect could also be explained as a result of the drug-induced abortion of disease-specific early natural (maladaptive) compensatory or decompensatory mechanisms. If indeed established as a disease-modifying agent in early PD, of course, we will need to prove that it can also modify the disease progression in the premotor phase, by delaying the development of possible PD into probable PD, using the above mentioned delayed start design to warrant the use in this very early stage.

**Expert commentary**

Nonmotor symptoms of PD have recently gained increasing attention as it has become apparent that understanding these symptoms as part of the spectrum of extranigral nondopamine-related symptoms may facilitate earlier diagnosis. Although nonmotor symptoms can present after motor symptoms, they often predate the cardinal signs of PD by many years, in keeping with the Braak hypothesis. Motor symptoms reflecting synucleinopathic involvement do not become evident until stage 3 of the 6 stages suggested by Braak. Yet, current scales used to assess PD patients, including the Unified Parkinson Disease Rating Scale (UPDRS), do not include items related to motor symptoms. This is particularly unfortunate given the emerging evidence that disease-modifying therapies may confer some benefit early on in the course of the disease. As a result, the onus will be on neurologists and other clinicians to have a high index of suspicion regarding nonmotor symptoms in patients at risk for, or showing early signs of, PD. Vigilant and proactive assessment of a patient with PD is especially critical in those with unexplained hyposmia, sleep abnormalities and neuropsychiatric and/or autonomic symptoms suggestive of a possible PD prodrome. As the premotor phase of PD is better understood, insight will be gained about appropriate use of disease-modifying and symptomatic agents during this early stage of disease.

**Five-year view**

The proper identification of the premotor phase of PD, coupled with evidence-based intervention, is likely to increase the lifespan of patients and to reduce disability. Clinical experience and research data are beginning to reveal more about the PD prodrome, and neuropharmacological research and drug development are occurring in parallel to identify potentially disease-modifying therapies. Early detection and intervention for PD has the potential to improve quality of life and treatment outcome, and to reduce cost and functional disability, and efforts are needed to address these unmet needs.

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**Key issues**

- Nonmotor symptoms comprise the premotor or prodromal phase of Parkinson's disease (PD), and consist of symptoms affecting autonomic, sensory, neuropsychiatric and sleep-related functions.
- These symptoms cannot be explained by the nigrostriatal degeneration that underlies motor symptoms, but may be related to pathological synucleinopathy that is evident long before motor symptoms emerge.
- The availability of disease-modifying treatments will necessitate early diagnosis of the premotor phase so optimal benefit can be obtained and long-term outcome can be improved.
- We propose new criteria for diagnosing this disorder and to enable treating those patients with future disease-modifying antiparkinsonian agents.
- In case of unexplained hyposmia or another potentially PD-related nonmotor symptom (rapid eye movement sleep behavior disorder, autonomic dysfunction or neuropsychiatric disorder) or in case of one of the cardinal signs of motor parkinsonism (i.e., bradykinesia, rigidity and resting tremor), two positive unrelated ancillary tests might be considered satisfactory proof to diagnose a clinically possible idiopathic PD.
- A clinically probable PD might be defined by a positive functional dopaminergic PET or single photon-emission computed tomography scan, in combination with two PD-related nonmotor symptoms plus one of the cardinal signs of motor parkinsonism, or in combination with two of these motor symptoms.
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Review

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