8 Non-Motor Symptoms in Parkinson's Disease

Dr R Fackrell,[1] Dr *J V Hindle*[2] *and Professor KR Chaudhuri*[3]

1. Consultant Physician, Royal United Hospitals' NHS Foundation Trust, Combe Park, Bath
2. School of Medical Sciences, University of Bangor, and Llandudno Hospital, North Wales
3. University Hospital Lewisham, London, National Parkinson Foundation Centre of Excellence, Kings College, London, Institute of Psychiatry and King's Health Partners

Introduction

Parkinson's disease (PD) can be seen as a motor disorder, with characteristic motor symptoms being present in the untreated and treated condition, combined with non-motor symptoms (NMS) which include neuropsychiatric symptoms, problems of arousal, autonomic symptoms, sensory symptoms and symptoms of mixed aetiology (table 1). PD results from degeneration of the substantia nigra pars compacta and the consequent dysfunction of the dopaminergic nigrostriatal pathway with additional involvement of serotonergic, noradrenergic and cholinergic pathways. It has been recognized that non-dopaminergic and non-motor symptoms are often present prior to diagnosis and these inevitably emerge with disease progression, impacting on morbidity, quality of life and mortality. The NMS of PD continue to be poorly recognized and inadequately treated in contrast with motor symptoms. A modern holistic approach to treatment of PD should include the recognition and assessment of NMS. This review gives a background of the pathogenesis and prevalence NMS complex of PD and a review of the management options for the NMS in PD which will be the main focus of the course presentation and attached slides. Although the neuropsychiatric disorders have been discussed in another chapter they are also discussed here because of their links with other NMS.

Background

Following the original description in 1817 of 'paralysis agitans' by James Parkinson,[1] through the 19th and 20th centuries, the motor disorder of PD has been researched extensively, resulting in improved diagnostic accuracy and the development of robust assessment tools for the motor dysfunction of PD. Many studies and clinical observations have suggested that NMS such as sleep disorders, cognitive problems and bowel and bladder disorders are common in PD. However, it is only recently that research has focused on the effect of NMS on quality of life, institutionalisation rates, health economics and mortality rates in PD.[2,3,4,5] NMS can be present even in early PD and can affect quality of life.[6,7] An older age of onset of PD is associates with a higher rate of olfactory and sensory symptoms, autonomic symptoms, sleep disorders, dementia and Psychosis.[8] PD is an example of an age related disease and the fact that NMS correlate with advancing age and disease severity suggests that these symptoms and their management will become increasingly important as the average life-expectancy of the population increases.[9,10] A prospective follow-up study (15–18 years) of 149 PD patients reported that the major disabling symptoms included cognitive decline, falls, hallucinations, depression, urinary incontinence, dementia and choking and were associated with an institutionalisation rate of 40%.[11] The NMS complex is frequently unrecognized by healthcare professionals due to physicians or nurses concentrating more on motor aspects, or lacking awareness that NMS are related to PD or because the symptoms are not declared to the healthcare professionals.[10,12] Work by the Parkinson's Disease Non Motor Group (PD-NMG) has led to the validation of the first comprehensive clinic-based self-completed NMS questionnaire and also a scale, the NMS scale that allows easy identification of NMS by the physician.[13] A recent international survey showed that up to 62% of NMS in PD might remain undeclared to health care professionals because patients are either embarrassed or unaware that the symptoms are linked to PD.[13] The use of a screening tool such as the Non-motor Symptoms questionnaire can help identify the problems.[14]

Most NMS have a poor response to dopaminergic therapy with other pathways, including the serotonergic and noradrenergic pathways, being implicated.[15] Braak and colleagues have introduced the concept of a six-stage pathological process, beginning at 'induction sites' with degeneration of the olfactory bulb and the anterior olfactory nucleus (clinically manifest as olfactory dysfunction) at stage

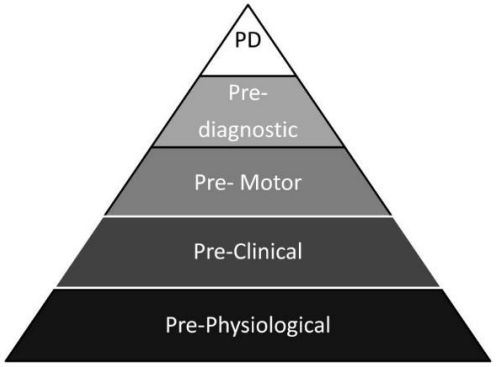
1, while stage 2 reflects progression of the pathological process to the lower brainstem.[16] The latter involves brainstem nuclei, which are thought to be key areas mediating NMS such as olfaction, sleep, homeostasis, constipation and central autonomic control. Several of these symptoms are now recognized as possible pre-motor features of PD. The typical clinical motor triad of PD emerges at Braak stages 3 and 4 with the involvement of the substantia nigra and other deep nuclei of the mid- and forebrain.[13] Limitations of the Braak hypothesis include the fact that Braak based his classification on Lewy body pathology and not neuronal cell loss and that it does not sufficiently explain the involvement of no-dopaminergic systems in the development of NMS.

Pre-Motor Non-Motor Symptoms

A wide spectrum of NMS has been described in PD, as shown in Table 1. Several NMS have been identified before the motor syndrome of PD emerges in Braak stage I and II associated with degeneration of the substantianigra.[17] In addition spinal cord lesions may also be associated with a spectrum of premotor autonomic symptoms in PD.[18]

In the future, pre-motor identification of 'at risk' individuals for PD may be based upon detection of some or a combination of NMS of PD. Examples include tests that combine olfactory abnormality detection with REM behaviour disorder (RBD) and functional imaging of the striatum (DAT Scan), or transcranial ultrasound imaging, which may show hyper-echogenicity of the nigra in PD.[19] It is postulated that there are four cardinal NMS that may predict development of PD, olfaction, REM sleep disorder, depression and constipation. Future research will help identify more biomarkers to enable the identification of very early disease in the pre-motor, preclinical and even pre-physiological stages of PD which have been proposed as the Parkinson's disease At Risk Syndrome (PARS) (Figure 1).[20] It is likely that non-motor symptoms will form components of the PARS pyramid. A meta-analysis has shown the strongest risk factors associated with later PD diagnosis are having a family history of PD or tremor, a history of constipation, and lack of smoking history.[21] One study has shown retrospectively that alpha-synuclein pathology was present in the colon of some people with PD suggesting that this would be worth exploring as a biomarker for premotor PD.[22] Another recent study has suggested that mild memory disorder, constipation or postural hypotension, depression or anxiety, visual hallucination or psychosis (in the elderly), and REM sleep behaviour disorder associated with low cardiac MIBG uptake could be used in prospective studies to predict PD.[23]

Figure 1 Parkinson's disease At Risk Syndrome[20]



NMS that result from non-dopaminergic pathology, such as olfaction, depression, autonomic dysfunction and RBD, are a target for the development of PD screening tests.[24] The onset of dopaminergic cell loss occurs years before the motor symptoms appear and at diagnosis there is a reduction of 60–70% of the dopaminergic neurons and a reduction of dopamine by 80%.[25] Screening of individuals at increased risk will be important if measures to slow the neurodegenerative process can be introduced at an early stage. Transcranial sonography (TCS) of the substantia nigra has been suggested as a possible screening tool for PD.[19] Studies have shown that more than 90% of PD patients have increased echogenicity of the substantia nigra that can be detected early in the disease.[19]

However, the findings need to be replicated at other centres before the widespread use of this technique.

Olfaction

Impaired olfaction is one of the earliest and most common NMS of PD and has been shown to affect up to 90% of PD patients.[26] Olfactory deficits have been reported in asymptomatic relatives of patients with PD, some of whom subsequently became symptomatic.[27] Of 78 first degree asymptomatic relatives of patients with non-familial PD, 40 had hyposmia at baseline and 2 years later 4 had clinical PD.[28] Using the Brief Smell Identification Test (BSIT) in 2263 healthy Japanese–American subjects, a relative odds ratio for PD in the lowest BSIT centile of 4.3 ($p = 0.02$) has been reported. A total of 163 patients had died, with autopsies showing 17 with incidental Lewy body disease.[29] In another study using DAT scan and transcranial sonography, 30 patients with idiopathic anosmia were investigated; of whom 11 had abnormal transcranial sonography (TCS) while 5/10 subjects had pathological DAT scans.[30] The pathophysiology is unclear but neuropathology and imaging studies have suggested structural and functional changes in the olfactory bulb.[31] One study linking olfactory disturbance with disturbances of pain perception has suggested a link with limbic dysfunction.[32] Olfactory testing aims to identify deficits in odour detection, odour identification, and odour discrimination. Odour detection and identification appear unrelated to disease stage or duration while odour discrimination is negatively correlated to severity of disease and may even be partially reversible after deep-brain stimulation.[33]

REM Behaviour Disorder

RBD is a parasomnia, characterised by loss of the normal skeletal muscle atonia during REM sleep, thus enabling the patient to physically enact their dreams and, in some, vocalisations and abnormal movements are reported by bed partners[34]. The pathogenesis of RBD is unclear; however, there is evidence that it may arise as a result of degeneration of lower brainstem nuclei, including the pedunculopontine and subcoeruleal nucleus, areas related to Braak stage 2.[35]

Table 1 Non-motor symptoms of Parkinson's disease

Neuropsychiatric	Mood disorders- depression, anxiety, panic attacks.
	Anhedonia
	Apathy
	Psychosis- Hallucinations, illusion, delusions
	Cognitive impairment
	Dementia
	Impulse control disorders
	Repetitive behaviour- punding
	Delirium (could be drug induced)
Sleep	Restless legs and periodic limb movements
	REM behaviour disorder and REM loss of atonia
	Non-REM sleep-related movement disorders
	Excessive daytime somnolence
	Vivid dreaming
	Insomnia
	Sleep disordered breathing
Autonomic	Genitourinary: Urgency, nocturia, frequency, erectile dysfunction
	Cardiovascular: Orthostatic hypotension, syncope, 'Coat hanger' pain
	Thermoregulation: Sweating, seborrhoea
	Dry eyes (xerostomia)
Gastrointestinal	Dribbling of saliva
	Loss of taste (ageusia)
	Dysphagia/ choking
	Reflux, vomiting
	Nausea
	Constipation
	Unsatisfactory voiding of bowel
	Faecal incontinence
Sensory	Pain
	Paraesthesia
	Olfactory disturbance
Others	Fatigue
	Diplopia
	Blurred vision
	Weight loss
	Weight gain (possibly drug induced)

Longitudinal data suggest that RBD may predate motor symptoms in up to 40% of patients.[36] A retrospective study of 44 patients with RBD revealed that 45% of patients developed a neurological disorder such as PD, multiple system atrophy (MSA) or dementia with Lewy body after a mean of 11.5 years.[37] Therefore, this study supports the suggestion that RBD is linked to preclinical PD. The combination of olfactory deficit and isolated RBD could be screened by DAT scan as a possible pre-motor testing for individuals at risk of developing PD.[38] The role of RBD as a potential marker of PD using colour vision, olfaction, motor speed testing, autonomic function and depression rating was studied in 25 patients with RBD and compared with controls.[39] In 50% of RBD patients who scored poorly in one test, performance was poor in other tests, suggesting that olfactory dysfunction and depression may occur concurrently in RBD.[39] More recently, the authors suggested that there is a 40% risk of developing a parkinsonian syndrome at 10 years in those who develop idiopathic RBD. RBD is common in early PD. It is important to recognise since it associated with increased severity and frequency of non-motor features, poorer subjective motor performance and a greater impact on health-related quality of life.[40]

Depression

Although the main subject of this section is the non-psychiatric non-motor symptoms of PD it is important to understand the relationship between depression and premotor PD. Depression is the most common psychiatric complication of PD and can affect 10–70% of PD patients[41] more often in conjunction with anxiety.[42] Depression may arise as a result of damage to serotonergic as well as limbic noradrenergic and dopaminergic neurotransmission.[43] The PROMS-PD study has confirmed that depression may also be particularly prevalent in PD associated with axial motor symptoms suggesting a possible association with cholinergic pathways and white matter disease.[44] Studies have suggested that depression, like RBD and hyposmia, may precede the development of PD.[45] Depressed people are more likely to develop PD than osteoarthritis or diabetes, while a retrospective cohort study reported that at the time of diagnosis of idiopathic PD, 9.2% had a lifetime diagnosis of depression compared with 4.2% of controls.[45] A PD test battery, including tests for depression (Beck Depression Inventory), olfactory testing (The University of Pennsylvania Smell Identification Test [UPSIT]) and a simple motor task of wrist flexion and extension, showed significant impairment in first-degree relatives of PD from controls.[46] There is evidence that certain cognitive styles and coping mechanisms can increase the risk of depression in PD.[47,48] These psychosocial influences on depression in PD impact as the disease progresses and may follow diagnosis but do not explain the occurrence of depression preceding the diagnosis of PD.

Constipation

Constipation is one of |he most common NMS and may precede the development of PD.[49] In a prospective study, the bowel habits of 6790 men were studied for 24 years showing that 92 developed PD and those with constipation had a threefold risk of developing PD after a mean interval of 12 years from initial constipation.[50] A study of the involvement of the gastrointestinal tract in PD in 98 patients reported that symptoms such as constipation, abnormal salivation, dysphagia and nausea were more common in PD patients than in controls.[51] Studies have also shown that constipation may be associated with a lifetime low frequency of bowel opening with reduced water intake and reduced thirst response.[52] Constipation in PD does not respond well to dopaminergic treatment, suggesting a non-dopaminergic mechanism in the pathogenesis.[49]

Other Non-motor Symptoms

Nocturnal NMS

Nearly all PD patients have sleep disturbances which usually start early in the disease.[53] The pathogenesis of sleep disruption is multi-factorial but degeneration of central sleep regulation centres in the brainstem and thalamocortical pathways is likely to be important. The pedunculopontine nucleus, locus coeruleus and the retrorubral nucleus, influence normal REM atonia and phasic generator circuitry and have been implicated in the pathogenesis of RBD.[54] One study has suggested a link between sleep dysfunction in PD and altered iron metabolism with excess deposition.[55] The range of sleep conditions that occur in PD are shown in Table 2. Other factors that may contribute to sleep disruption include motor symptoms, anxiety and depression, and dopaminergic treatment. Some NMS cause abnormalities in the primary sleep architecture and have a secondary effect on the quality of sleep, such as nocturia causing bedwetting if the patient is too rigid to get out of bed or restless legs syndrome causing frequent arousal. Obstructive sleep apnoea, not necessarily associated with obesity, and a narcoleptic pattern of rapid onset of sleep are also important causes of sleep-related morbidity in PD.[54]

Table 2 Sleep-related non-motor features of Parkinson's disease

Insomnia	Fragmentation of sleep
	Sleep-maintenance insomnia
	Sleep-onset insomnia
Motor function-related	Akinesia (difficulty turning)
	Restless legs
	Periodic limb movements of sleep
Urinary difficulties	Nocturia
	Nocturia with secondary postural hypotension
Neuropsychiatric/parasomnias	Depression
	Vivid dreams
	Altered dream content
	Nightmares
	Night terrors
	Sleep talking
	Nocturnal vocalisations
	Somnambulism
	Hallucinations
	Panic attacks
	REM behaviour disorder
	Non-REM-related sleep disorders
Treatment-related motor	Nocturnal off-period-related tremor
	Dystonia
	Dyskinesia
	Off-period-related pain/paraesthesia/muscle cramps
Urinary	Off-period-related incontinence of urine
Treatment-related motor	Nocturnal off-period-related tremor
	Dystonia
	Dyskinesia
	Off-period-related pain/paraesthesia/muscle cramps

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) and involuntary dozing affects up to 50% of PD patients and may be preclinical marker.[56] EDS is important to recognize as it may have a significant impact on quality of life in PD and is associated with poor concentration and memory, which may result in road accidents and accidents at work.[57] The phenomenon of sudden onset of sleep (SOOS) has been widely discussed and publicised particularly linked with dopamine agonists. The concept of a flip-flop switch has been suggested to be responsible for the sleep–wake cycle in primates. Dopaminergic dysfunction and neuronal degeneration can destabilize the switch and its regulators, promoting rapid transitions to sleep. Hypocretin, neuronal activity-related pentraxin (NARP) and dynorphin releasing neurones have also been implicated but not confirmed as having a regulatory role.[58]

Dysautonomia

Autonomic dysfunction is associated with various movement disorders, most commonly Parkinson's disease and MSA, and it can be an important feature in the differential diagnosis of Parkinsonian disorders.[59] The symptoms of dysautonomia in PD may include orthostatic hypotension, bladder dysfunction, gastrointestinal dysfunction (particularly constipation), sexual dysfunction and hyperhidrosis. The pathophysiology is complicated and is thought to include dysfunction or degeneration of the nucleus ambiguus, the dorsal–vagal nucleus and various medullary centres that modulate the activity of the sympathetic pre-ganglionic neurons (these include the rostral ventrolateral medulla, ventromedial medulla and the caudal raphe nuclei). Alpha-synuclein pathology can be detected in multiple organs in PD.[60] Modulation of the central autonomic network is thought to be disrupted through degeneration of cholinergic, monoaminergic and serotonergic nuclei. There is a

significant increase in orthostatic dizziness, bladder dysfunction (mainly urge incontinence and frequency), hyperhidrosis and erectile dysfunction in PD patients compared with controls.[61] Bowel dysfunction, including constipation and feeling full, are also common in PD patients.[61] Approximately 50% of PD patients rated the impact of the autonomic symptoms on their daily lives as 'a lot' or 'very much'. The NMSQuest study confirmed that dysautonomic symptoms were significantly more prevalent in PD patients than in controls, and the total number of non-motor symptoms correlated with the stage of the disease.[14] In a study using beat-to-beat blood pressure measurements during performance of the Valsalva manoeuvre to detect sympathetic neurocirculatory failure in PD patients, and 6-[18F] fluorodopamine to estimate sympathetic cardiac innervations, it was found that all 9 of the PD patients who had sympathetic neurocirculatory failure, and 11 of the 15 PD patients who did not have neurocirculatory failure, demonstrated sympathetic cardiac denervation, relative to controls. This contrasted dramatically with the results from MSA patients, who did not show evidence of sympathetic cardiac denervation. The results suggest that cardiac denervation is not related to severe or late-stage disease and catecholamine function in PD may be defective not only in the brain but also in the heart.[62] Meta-[123I]-iodobenzylguanidine (MIBG) is a noradrenaline analogue, taken up by postganglionic sympathetic neurons, and has been used to analyze the sympathetic cardiac activity in PD patients with orthostatic hypotension. It has been found to be reduced in patients with PD, both with and without orthostatic hypotension and differs from MSA, in which cardiac MIBG uptake is usually normal.[63] Reduced cardiac sympathetic innervation is associated with symptoms of autonomic dysfunction in PD.[64] Nocturia, frequency and urgency are common complaints in PD patients and functional imaging studies show that dopaminergic mechanisms may be involved in bladder control.[65] There is evidence of Lewy body pathology in the bowel and it has been suggested that much of the bowel dysfunction in PD is related to peripheral mechanisms whereas the urinary dysfunction is more related to central mechanisms linking frontal control centres to the pontine micturition and storage centres.[66] Identification of those with dysautonomia is important in order to avoid falls and other complications but also because it is associated with reduced survival.[67]

Fatigue

Fatigue is a common complaint in Parkinson's disease and is reported to have a negative impact on the quality of life.[68] Fatigue may be related to other non-motor features of PD such as depression, sleep disturbances and dementia.[68] However, studies have shown that fatigue is a non-motor phenomenon, which may occur independently of other non-motor symptoms.[69]

Sexual dysfunction

Both reduced and increased sex drive have been reported in PD,[70] and it is thought that this may represent another dysautonomic symptom of the disease. Testosterone deficiency has been implicated in this process and testosterone replacement therapy improved a range of motor and non-motor symptoms in a trial of ten PD patients with signs of testosterone deficiency.[71] Hypersexuality and other forms of aberrant sexual behaviours and drive are part of the impulse control disorders, which occur with dopaminergic drug treatment.[72]

Pain

Pain is in PD is under-recognised and often inadequately treated.[73] Pain is one of the major clinical symptoms in PD but its pathophysiology is unclear. Medial and lateral pain syndromes are recognized and medial pain pathways are composed of parabrachial nucleus and locus coeruleus projecting to the secondary somatosensory cortex and the anterior cingulate, thus suggesting that there may be a link between early PD and pain.[74] Various pain syndromes described may be related to motor fluctuations, early morning dystonia or secondary causes such as musculoskeletal pain. In some cases retroperitoneal fibrosis related to use of some ergot dopamine agonist may present as deep visceral pain. Oral (burning mouth syndrome) and genital pain may rarely occur and needs to be recognized. A four stage taxonomy has been proposed by one group to distinguish pain syndromes in PD in order to aid management.[75] Another group identified five types of pain in a PD cohort and proposed a treatment algorithm.[76]

Drug-Induced NMS and 'Wearing Off' Phenomenon

PD patients on long-term levodopa treatment may experience the 'wearing-off' phenomenon, which may be associated with NMS such as anxiety, pain, tingling, coldness of limbs, restless legs and 'unclear thinking'. 17% of patients experience non-motor symptoms associated with the wearing-off phenomenon, which include sensory dyspnoea, nausea, facial flushing, hunger and pain.[77] A specific wearing-off patient questionnaire has been developed to aid clarification and better definition of the wearing-off-related motor and NMS in PD.[78]

Management of Non-Motor Symptoms

There are few robust controlled studies for the treatment of NMS in PD and virtually none for the treatment of dysautonomia in PD.[79] Moreover, the effect of these treatments on quality of life in PD is lacking, and many trials include only small numbers of patients. The Movement Disorder Society have produced an evidence based review which included the management of the neuropsychiatric disturbances.[79] Many detailed and research based autonomic tests can be performed,[80] but this review focusses on practical day to day management.

Sleep disorders

Small trials to appeared to support the use of modafinil for EDS in PD,[81,82] however, a larger double-blind, placebo-controlled trial in 40 patients did not show efficacy of modafinil for EDS in PD.[83] The quality of the studies and conflicting results suggest that there is not enough evidence to support its use. The use of modafanil was not supported in the NICE guidelines and recent licensing restrictions have effectively prevented its use in PD. Anyone with unpredictable EDS or SOOS should be counselled about not driving or operating machinery. There are no controlled trials for treatment of RBD but night-time dosing with levodopa and use of clonazepam or pramipexole may reduce involuntary nocturnal movements during sleep.[36] Most clinical experience is based on use of clonazepam which can be extremely helpful. It is necessary to exercise caution as sleep-disordered breathing may coexist with RBD and can be worsened by clonazepam. The starting dose is 250-500 micrograms, increasing according to response normally to a maximum of 2mg at bedtime.

Autonomic function

Controlled trial evidence regarding the treatment of most autonomic problems in PD is limited with much of available guidance being based on expert opinion and good practice.

Drooling

Drooling should be managed by a multidisciplinary team starting with a conservative approach. Speech and language therapists can advise on specific positioning and techniques to promote regular swallowing including the use of prompting devices.[84] Botulinum toxin type A or B injected into the parotid and/or submandibular glands can be an effective treatment for drooling.[85] Oral glycopyrrolate has been used to treat hyper-salivation in children with cerebral palsy and it has been suggested as a possible unlicensed option in PD.[86] Glycopyrrolate has to be hospital specialist prescribed and the tablets are not listed in the BNF. In current practice prescription of glycopyrolate liquid is considerably cheaper than tablets. The current starting dose is 1mg three times daily, increasing as necessary to 2mg three times daily. There is insufficient evidence to support the use of ipratropium bromide. Hyoscine hydrobromide patches and atropine drops should not be used due to the risk of developing hallucinations and other significant anticholinergic side effects.

Dysphagia

Basal ganglia, brain stem and cortical dysfunction as well as pathology in the enteric nervous system contribute to dysphagia in PD.[87] Dysphagia occurs in both oral and pharyngeal phases in PD.[80] Dysphagia should be managed by a multidisciplinary team. Causes of dysphagia should be appropriately investigated to ensure there are no causes other than PD. The involvement of a speech and language therapist is vital. Assessment may include the use of video fluoroscopy and upper gastrointestinal endoscopy, endoscopic evaluation of swallowing and oesophageal manometry.

Alteration of the consistency of food and drink, advice on the organisation of the bolus of food within the mouth and on the frequency of swallowing can be helpful. Exercises to promote tongue strengthening, tongue control and voice exercises may also be helpful.[88]

Delayed Gastric emptying

PD is associated with slowing of the whole gastrointestinal tract. Delayed gastric emptying is comment in PD and occurs at all stages. It is under-recognised but is important not to miss since it can contribute to many upper gastrointestinal symptoms and contribute to poor absorption of PD drugs.[89] Delayed gastric emptying may be due to infiltration of the enteric nervous system by alpha-synuclein pathology, humoral changes and the contribution of PD drugs. Therapeutic strategies for delayed gastric emptying are limited. The standard treatments in those without PD are dopamine antagonist drugs such as metoclopramide the use of which is precluded in PD. Domperidone may be useful but there are no studies to support its use and it is not licensed. Caution should also be employed with the use of domperidone as it can prolong the QT interval. Macrolide antibiotics may increase gastric emptying but cannot be used long term. Ghrelin is theoretically useful but is currently experimental[89] and a pilot trial of nizatidine, a selective histamine H2-receptor antagonist, has been published.[90]

Constipation

In the management of constipation it is important to ensure that there is no other cause such as hypothyroidism or bowel pathology. A recent change in bowel habit particularly associated with anaemia requires further investigation. The presence of a sigmoid volvulus may be suggested by recurrent total constipation with abdominal distension. Iatrogenic causes should be excluded particularly concurrent use of opiate analgesics. It may be useful to distinguish between colonic dysmotility with high faecal loading and anorectal dysfunction with loading of the rectum although it is not clear whether an abdominal X-ray is justified. There is little research available for treatment of constipation, however, in one study, macrogols were shown to be more effective than lactulose[91] and there is also low quality evidence to support the use of psyllium.[92] Improving mobility and encouraging exercise, increasing fibre intake to more than 15 grams per day with at least 1.5 litres of fluid are the mainstays of treatment of colonic dysmotility. Anorectal dysfunction can be exacerbated by the use of laxatives which may cause faecal soiling. Dopaminergic medication may help improve anorectal dysfunction. Other methods of treatment that have been tried include defaecation training, puborectalis botox and sacral nerve stimulation[66] and abdominal massage. For women with chronic constipation who have not responded to two laxatives in highest dose for at least 6 months the serotonin-4 (5-HT_4) receptor agonist prucalopride may be considered although there are no trials specifically in PD.[93] Prucalopride may theoretically improve gastric emptying.[89]

Genito-urinary symptoms

There is a variable effect of PD drugs on bladder function but in general bladder symptoms may improve with improved control of PD. Patients should be investigated for UTI, undergo behavioural evaluation of drinking and voiding habits, and modification, if applicable.[94] In managing bladder problems in PD it is most important to check a post-void volume (PVV) since at diagnosis a residual of >100ml is suggestive of a diagnosis of MSA rather than PD. PVV is also important in monitoring the response to treatment and avoidance of retention. Formal urodynamic testing may also be considered. Urinary frequency is often due to an overactive detrusor in PD and should be considered for treatment with an anticholinergic drug that does not cross the blood brain barrier (tolterodine and trospium are better options than oxybutinin in this respect). Mirabegron, a β_3-adrenoceptor agonist, is a new class of drug for detrusor over-activity and since it has no anticholinergic activity and no cognitive effects may be theoretically useful in PD but evidence for its comparative benefit is lacking.[95] There are no trials of detrusor botulinum toxin injections in PD but this may be considered as a minimally invasive option.[94] Retention of a residual of >100ml is more likely to require intermittent self catheterisation In the presence of incontinence or very significant retention permanent urinary catheter may need to be considered, with this being more commonly needed in MSA.[65] Erectile dysfunction should be appropriately investigated and managed through a specialist

team.[96] Erectile dysfunction can be treated effectively in PD with the use of sildafinil without the occurrence of side effects, in particular postural blood pressure[97] and apomorphine can be used.[96]

Orthostatic hypotension

It is important to consider the possibility of orthostatic hypotension as a cause of dizziness, falls, syncope, lethargy, fatigue, confusion, visual disturbances and even angina like pain. It can cause discomfort and heaviness over the neck and shoulders known as coat-hanger pain. Regular checks of blood pressure in clinic should include a check of lying and standing blood pressure with recordings done up to 3 minutes after standing. More specific testing includes measurement of R-R 30:15 interval on ECG, responses to deep breathing, cold pressor, valsalva manoeuvre or isometric exercise. Standard head-up tilt testing can also be useful.[80] The single most useful test is a 24 hour blood pressure monitor. This may demonstrate a reversal of the normal diurnal pattern with daytime hypotension and night time hypertension.

A stepwise systematic approach to the management of orthostatic hypotension can improve function in PD.[98] Management includes avoidance of sudden standing and large meals (table 3). It is now clear that orthostatic hypotension does not occur alone in PD and most patients will have variable blood pressure and will often have supine and nocturnal hypertension[99,100] which can be associated with end organ damage and white matter changes in the brain.[101] Following conservative measures, most specialists opt for first line domperidone (taking into account recent advice regarding prolonged Q-T interval on ECG) and then considering fludrocortisone to a maximum of 400 micrograms per day. The latter is often associated with fluid retention and leg oedema. Midodrine is now recommended in the NICE guidelines as first line therapy. Midodrine can cause supine hypertension which may limit its safety and all patients treated should have regular checks of supine blood pressure preferably through 24 hour blood pressure recordings. The management of hypotension and hypertension in PD can be very tricky[102.]and in some circumstances day time midodrine (given before 6pm) has been combined with night time GTN patch or other short acting vasodilator or calcium channel blocker to combat nocturnal hypertension.[103] L-DOPS (droxidopa) is a pro-drug of noradrenaline and adrenaline and may have both a peripheral and a central effect. The evidence suggests that this drug may be better tolerated than other preparations[104] although one recent small study failed to show benefit.[105] The Food and Drug Administration's (FDA) Cardiovascular and Renal Drugs Advisory Committee has approved the use of droxidopa in January 2014 for patients with primary autonomic failure, dopamine beta hydroxylase deficiency and non-diabetic autonomic neuropathy. In the UK droxidopa is available only to registered users and has to be imported from Japan. There is emerging evidence, particularly in the management of Systolic Hypertension Orthostatic Hypotension syndrome that pyridostigmine may be beneficial. Pyridostigmine is a cholinesterase inhibitor that improves ganglionic neurotransmission in the sympathetic baroreflex pathway. Because this pathway is activated primarily during standing, this drug improves orthostatic hypotension and total peripheral resistance without aggravating supine hypertension. Because the pressor effect is modest, it is most adequate for patients with mild to moderate orthostatic hypotension.[106,107]

Table 3 Conservative management of orthostatic hypotension

Method	***Comment***
Avoid sudden head up/stool strain	Early morning after nocturnal polyuria
Avoid large meals and alcohol	Vasodilatation
Adequate fluid and salt intake	Plasma volume
Avoid excessive heat	Intravascular volume / vasodilatation
Elevate bed head $20\text{-}30^0$	Reduce renal artery pressure and increased renin
Elastic stockings	Venous pooling
Avoid vasoactive drugs	Psychotropics

Sweating

Excessive sweating can be very problematic in PD although treatment options are few. It may be associated with fluctuations or dyskinesia and may in theory improve with better motor control. Topical treatments are rarely appropriate since the sweating is not localised. Systemic therapy with anticholinergics such as oxybutinin can be effective outside PD but may be limited by side effects in PD. One unlicensed preparation Glycopyrrolate does not cross the blood brain barrier and warrants further study.

Effects of Parkinson's Treatment

Although deep-brain stimulation of the subthalamic nucleus is an effective treatment for motor symptoms of PD, its effect on non-motor symptoms is unclear. Dopaminergic therapy appears to be unhelpful for most of the NMS of PD unless these are linked to motor fluctuations. Many NMS of PD may have a non-dopaminergic basis and symptoms usually do not respond to dopaminergic treatment. Indeed, dopaminergic therapy may precipitate some non-motor problems in PD such as orthostatic hypotension.

Conclusions

Delayed detection of NMS may lead to disability and poor quality of life, increasing the cost of care of PD in the society. NMS such as visual hallucinations, dementia and falls are a major source of hospitalization and institutionalization. Recognition of non-motor symptoms is therefore essential for the holistic management of PD and the importance of a multidisciplinary approach, including support for carers, cannot be overemphasised.

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