# Treatment of dysautonomia in extrapyramidal disorders

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***Abstract*:** Although extrapyramidal diseases are commonly thought to solely affect the extrapyramidal motor system, nonmotor symptoms such as behavioural abnormalities, dysautonomia, sleep disturbances and sensory dysfunctions are also frequently observed. Autonomic dysfunction as an important clinical component of extrapyramidal disease (idiopathic Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies) is often not formally assessed and thus frequently misdiagnosed. Symptoms of autonomic dysfunction in general impact more on quality of life than motor symptoms. Appropriate symptom-oriented diagnosis and symptomatic treatment as part of an interdisciplinary approach can greatly benefit the patient. Unfortunately, double-blind, randomized, controlled studies are scarce with the consequence that most recommendations are not based on the highest level of evidence. This review elaborates a limited overview on the treatment of cardiovascular, gastrointestinal, urogenital and sudomotor autonomic dysfunction in various extrapyramidal syndromes.

***Keywords*:** autonomic dysfunction, dysautonomia, extrapyramidal disease, multiple system atrophy, Parkinson's disease, treatment

## Introduction

Parkinson's disease (PD) and other extrapyramidal disorders are clinically characterized by motor symptoms such as bradykinesia, rigidity, tremor and postural instability [Parkinson, 1817]. Although the clinical diagnosis is based on these cardinal symptoms, there is increasing evidence that many clinical symptoms of PD are unrelated to the motor functional system. These 'nonmotor' symptoms, which include behavioural, sleep or perception dysfunctions as well as dysautonomia [Reichmann and Ziemssen, 2009; Ziemssen and Reichmann, 2007; Ziemssen *et al.* 2006], present as early signs of the disease frequently dominating the overall clinical picture [Witjas *et al.* 2002]. As early as 1817 James Parkinson already described the reoccurrence of autonomic regulatory disorders in his 'Essay on the shaking Palsy' and postulated a 'mysterious sympathetic influence' [Parkinson, 1817]. Onehundred years later Lewy described rigor, tremor and 'sympathetic dysfunctions' as typical Parkinson's symptoms, complemented by 'incontinence, salivation, lacrimation, rhinorrhoea, oedemas, and cyanosis of one or several extremities, Stellwag's and Graefe's, one- or both-sided sweating' [Lewy, 1913]. Atypical parkinsonian disorders like multiple system atrophy (MSA) are characterized by pronounced early autonomic dysfunction [Wenning *et al.* 2000].

## Autonomic nervous system

The autonomic nervous system subconsciously controls various functions of our body in order to maintain homeostasis. Hence, every organ in the human body is connected to the autonomic nervous system and consequently regulated by it. Various areas in the brain form a central autonomic network. Incoming information from the periphery (autonomic afference) is processed and a response is transmitted to the peripheral target organs (autonomic efference). The efferent autonomic system is divided into two different components, the sympathetic and parasympathetic part.

To maintain homeostasis, the autonomic nervous system comprises numerous autonomic reflex circuits each consisting of an afferent, a central processing and an efferent component. The afferent signal mainly originates from specialized sensors; for example, the baroreceptor, which

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register changes in biological equilibrium and convert them into neural activity. Central autonomic centres compare the afferent signal to reference values and subsequently, generate an efferent response which is transmitted to effector organs of the control loop (e.g. medial layer of vasculature). The effector organs assist in correcting the dysfunctional condition which has been mapped by the sensor.

## Parkinson's disease and dysautonomia

The prevalence of dysautonomia in PD varies between 14% and 80% depending on the population and methodology. More than 50% of PD patients report impairment of daily life [Appenzeller and Goss, 1971]. The occurrence of dysautonomia increases as disease progresses, thereby impacting on the subjective picture of the symptoms, quality of life and the treatment of the disease [Sakakibara *et al.* 2008; Jost, 2003]. The almost ubiquitous loss of neurons and the appearance of Lewy bodies within completely different parts of the nervous system are thought a primary cause of this dysautonomia. Braak *et al.* observed the occurrence of lesions in the dorsal vagal nucleus and in other autonomic cerebral stem centres of PD patients before manifestation of clinical symptoms and of characteristic histopathological changes in the subtantia nigra [Braak *et al.* 2004]. Dysautonomia also occurs secondary to widespread diseases such as diabetes mellitus. In this case, optimization of treatment of the underlying disease is crucial. In addition, there is a high prevalence of drug-induced dysautonomia [Thanvi and Lo, 2004; Polinsky, 1990]. Particularly psychotropic drugs which are commonly used in patients with extrapyramidal disorders exhibit anticholinergic or antiadrenergic effects [Korchounov *et al.* 2004; Jost, 1997]. Antiparkinsonian medication is also thought to affect autonomic function [Ziemssen and Reichmann, 2007].

## Atypical parkinsonian syndromes and dysautonomia

MSA is a sporadic neurodegenerative illness that is clinically characterized by a combination of extrapyramidal, autonomic, cerebellar and pyramidal tract signs and histological neuron loss, gliosis and glial cytoplastic inclusion bodies [Wakabayashi and Takahashi, 2006]. MSA is an important differential diagnosis that must be considered, especially in early dysautonomia. MSA subtypes (MSA-C and MSA-P) only differ little in their autonomic phenotype [Schmidt *et al.* 2008a]. Usually, MSA starts at a younger age than PD, and autonomic dysfunction begins earlier in the course of the illness. In an investigation of Magalhaes *et al.* all MSA patients had some degree of autonomic dysfunction in life whereas dysautonomia was absent in 24% of PD patients [Magalhaes *et al.* 1995]. Although each of the autonomic function systems was affected in variable numbers of PD patients, autonomic dysfunction in MSA generally involved more autonomic domains than in PD, and to a more severe degree, in particular with regard to inspiratory stridor [Reimann *et al.* 2009]. So the presence of autonomic disturbance alone does not distinguish between MSA and PD in individual cases. However, the presence of severe autonomic dysfunction, of autonomic dysfunction preceding parkinsonism, or of inspiratory stridor, are all individually suggestive of MSA.

Although autonomic dysfunction is accepted to be an important clinical symptom in MSA and PD patients, the role of autonomic dysfunction in progressive supranuclear palsy (PSP) patients is still quite unclear because of contradictory data on this issue [Kimber *et al.* 2000; Wenning *et al.* 1999]. As we have recently shown, 71% of PSP patients presented with pathologically small pupils in darkness at least in one eye in comparison to 32% MSA, 16% PD patients and 7% healthy controls [Schmidt *et al.* 2007]. In an additional study, we could demonstrate that PSP patients frequently present with significant autonomic dysfunction [Schmidt *et al.* 2008b]. The parasympathetic cardiovascular system seems to be involved to a similar extent in PD and PSP patients, whereas sympathetic cardiovascular dysfunction is more frequent and severe in PD patients, but can also be found in PSP patients.

Dementia with Lewy bodies (DLB) is thought to be the second most common subtype of dementia. DLB's typical symptoms include cognitive impairment, visual hallucinations, spontaneous parkinsonism, and fluctuating confusion in addition to autonomic failure [Hanson and Lippa, 2009]. Autonomic dysfunction is more severe in DLB than in PD [Oka *et al.* 2007a; Kaufmann *et al.* 2004; Thaisetthawatkul *et al.* 2004].

## Pathophysiology of dysautonomia

Modern technology allows comprehensive assessment of the autonomic nervous system. Scintigraphy uses $^{123}$I-metaiodobenzylguanidine

(MIBG) which is taken up by postganglionic adrenergic neurons like norepinephrine. Mitsui *et al.* investigated more than 250 PD patients applying scintigraphy. They observed a significant reduction of MIBG uptake in cardial sympathetic efferences irrespective of disease severity (Hoehn and Yahr), disease duration, treatment and pre-existing dysautonomic signs [Mitsui *et al.* 2006]. In addition, MIBG showed markedly decreased myocardial uptake in patients with DLB and pure autonomic failure, (PAF) which is a common feature of Lewy-body diseases like PD [Nakajima *et al.* 2008]. Positron emission tomography using $^{18}$F-dopa revealed loss of cardial postganglionic sympathetic innervation whilst $^{18}$F-dopa-concentration remained unchanged in liver, spleen and nasal mucosa [Goldstein *et al.* 2000].

Conclusively, dysfunction of postganglionic sympathetic efferences is regarded as primary cause of dysautonomia in PD. Unlike PD, postganglionic lesions are not present in MSA. MIBG scintigraphy, which is commonly used in cardiology and diabetology, is a valid tool to discriminate between PD and MSA [Kollensperger *et al.* 2007]. Cardiodenervation is accompanied by histologically proven neuronal loss and the presence of Lewy bodies in peripheral parts of the sympathetic nervous system in PD (e.g. sympathetic paravertebral ganglia, loss in tyrosine hydroxylase in the epicardia) [Braak *et al.* 2006]. Further phenotypic characteristics are significantly reduced serum epinephrine and hypersensitivity of adrenergic neurons with resultant hypertension [Goldstein, 2003].

In conclusion, while MSA patients feature pronounced central autonomic abnormalities PD patients are predominantly characterized by postganglionic sympathetic dysfunction (Table 1) [Goldstein, 2003]. In DLB, autonomic dysfunction may result from preganglionic dysfunction in addition to postganglionic dysfunction [Oka *et al.* 2007b]. In PSP, significant pathologies in autonomic brainstem centres of PSP patients have already been demonstrated [Rub *et al.* 2002].

## Cardiovascular system: orthostatic hypotension

Orthostatic hypotension is the most frequent symptom of cardiovascular autonomic dysfunction [Robertson, 2008; Peralta *et al.* 2007]. About 50% of PD patients with advanced disease and the majority of MSA patients complain about common symptoms of orthostatic hypotension such as dizziness, lightheadedness, and nausea or pain during standing [Bleasdale-Barr and Mathias, 1998]. Orthostatic hypotension results from a dysfunction of the sympathetic noradrenergic innervation of the cardiovascular target organs [Goldstein *et al.* 2002]. Importantly, symptoms of orthostatic hypotension may also be caused by dehydration or drugs such as dopamine agonists and selegiline [Churchyard *et al.* 1997]. Postprandial hypotension usually occurs 30–50 minutes after food intake while typical stress-induced orthostatic hypotension is evoked

**Table 1.** Classification of autonomic dysfunction in patients with synucleopathies. Modified from Goldstein [2003]. Different involvement of different autonomic functional system (preganglionic, postganglionic) and presentation with extrapyramidal and Parkinson-plus symptoms in patients with multiple system atrophy (MSA), idiopathic Parkinson's disease (PD), pure autonomic failure (PAF) and dementia with Lewy bodies (DLB).

| | Preganglionic dysautonomia | Postganglionic dysautonomia | Extrapyramidal dysfunction | Parkinson-plus-dysfunction (e.g. cerebral/ pyramidal dysfunction) |
|---|---|---|---|---|
| Multi system atrophy – Parkinson's-type (MSA-P) | ■ | | ■ | |
| Multi-system atrophy – cerebellar type (MSA-C) | | | | ■ |
| Multi-system atrophy – mixed type (MSA-M) | | | ■ | |
| Idiopathic Parkinson's disease (PD) | | ■ | | |
| Pure autonomic failure (PAF) | | | | |
| Dementia with Lewy bodies (DLB) | | ■ | ■ | ■ |

by physical exercise in PD [Chaudhuri *et al.* 1997; Jansen and Lipsitz, 1995].

The American Autonomic Society defines orthostatic hypotension as constant decrease of the systolic blood pressure to ≥20 mmHg and of the diastolic blood pressure to ≥10 mmHg within 3 min of postural change from a lying into a standing position [Kaufmann, 1996]. Orthostatic hypotension is *asymptomatic* when the patient does not develop any symptoms, or is *symptomatic* when the patient experiences dizziness, weakness, nausea, pain or impaired vision in response to postural change. To account for symptomatic and asymptomatic orthostatic hypotension Robertson suggested the 'standing time' as practical clinical diagnostic parameter [Robertson, 2008]. Standing time is defined as the period from getting up until orthostatic symptoms occur. According to Robertson's definition, a standing time of less than 30 seconds reflects severe impairment, while a standing time of more than 1 minute usually allows for an independent life. Factors like heat, food and alcohol intake, exercise, certain drugs (e.g. vasodilators) and activities which increase intrathoracic pressure (e.g. defecation, coughing) can worsen an asymptomatic orthostatic hypotension [Schmidt *et al.* 2009b].

## Treatment of orthostatic hypotension

There are alternative strategies for treatment of symptomatic orthostatic hypotension when rehydration therapy and modification of antiparkinsonian medication fail to relieve symptoms (Box 1). These therapies are used depending on their implementation levels and acceptance also in combination, irrespective of the severity of orthostatic hypotension. For example, if the patient predominantly complains about postprandial hypotension it is suggested to increase the frequency of meals while decreasing the portion size and to administer carbohydrates evenly across the day. If orthostatic hypotension is caused by drug-induced hypovolaemia (e.g. cardiovascular medication, psychiatric drugs, selegiline) it may be reversed by adjusting the dosage or by discontinuing the medication. If the condition is caused by prolonged bed rest, improvement may occur by sitting up with increasing frequency each day. Susceptible people should not sit down or stand up rapidly or remain standing still for long periods. Wearing fitted elastic stockings up to the waist may help reduce pooling of blood in the leg veins.

**Box 1.** Nonpharmacological and pharmacological treatment of orthostatic hypotension.

**Nonpharmacological procedures**

- Avoid sudden posture changes, particularly after long periods in supine position or during venodilating conditions (i.e. hot baths).
- Increase of daily salt (3–6 g NaCl) and water (2–3 l) intake.
- Diet low in carbohydrates; increase of meal frequency while meal size should be decreased.
- Isotonic exercise such as swimming, aerobic training, bicycling or walking at moderate level.
- Application of counter manoeuvres such as squatting or 'derby chair'.
- Wearing of elastic stockings or an elastic suit.
- Raised upper body position during sleeping (15–30 cm).

**Pharmacological procedures**

***Increase of blood volume***

- Fludrocortisone initial dose of 0.1–0.2 mg/d; up to a max of 1 mg/d. Caution: cardiac insufficiency, hypocalcaemia, oedema [Schoffer *et al.* 2007].
- Erythropoietin 4000 IE s.c. twice a week. Caution: iron substitution; increase in haematocrit; hypertension [Kawakami *et al.* 2003].
- Desmopressin nasal application via pump spray, particularly indicated in nycturia. Caution: hyponatraemia, hypertension [Mathias *et al.* 1986].

***Increase of peripheral vasoconstriction***

- Midodrine three times 2.5–10 mg/d, up to a max 40 mg/d; administration not later than 5 pm. Caution: supine hypertension, pruritus [Lamarre-Cliche *et al.* 2008].
- Ephedrine three times 12.5–25 mg/d. Caution: tachycardia, tremor, supine hypertension [Wittbrodt and Kovalick, 1999].
- Yohimbine two to three times 8 mg/d p.o. Caution: diarrhoea, nervousness, panic attacks [Sharabi *et al.* 2008].
- Caffeine 250 mg (=2 cups of coffee) in the morning. Caution: tachyphylaxia [Dewey *et al.* 1998].

***Various:***

- Metoprolol 12.5–100 mg/d p.o. or pindolol in concurrent bradycardia two to three times 2.5–50 mg/d p.o. Caution: hypotension, bradycardia, cardiac insufficiency [Cleophas *et al.* 1986].
- Clonidine twice 0.1–0.3 mg/d p.o. or one plaster per week. Caution: dry mouth, bradycardia, hypotension [Victor and Talman, 2002].
- Dihydroxyphenylserine (DOPS) twice 250–500 mg p.o.; especially recommended for dopamine-β-hydroxylase deficiency [Goldstein, 2006; Mathias *et al.* 2001; Victor and Talman, 2002].

Antidiuretic hormones such as fludrocortisone may be administered to PD and MSA patients experiencing severe symptoms [Maule *et al.* 2007]. However, the use of these hormones increases the risk of heart failure particularly in individuals with manifest heart disease. To limit the loss of potassium by fludrocortisone supplementation is indicated. Midodrine is considered as first line drug for treating orthostatic hypotension [Freeman, 2008]. It may be taken in combination with fludrocortisone to prevent the steep decline of blood pressure [Lamarre-Cliche *et al.* 2008]. Midodrine constricts arterioles thereby increasing resistance to blood flow. In the 1950s it was found that an artificial aminoacid, 3,4-threo-dihydroxyphenylserine (DOPS), was converted to norepinephrine (NE) in a single step by the enzyme L-aromatic amino acid decarboxylase (AADC), bypassing the need for the rate-limiting enzyme dopamine beta hydroxylase. Trying to replicate the success of dihydroxyphenylalanine (DOPA) in the treatment of PD, treatment with DOPS was attempted in patients with autonomic failure who have impaired NE release. DOPS improved orthostatic hypotension in patients with familial amyloid polyneuropathy, congenital deficiency of dopamine beta hydroxylase, PAF and MSA [Mathias *et al.* 2001].

Supine postprandial hypotension complicates extrapyramidal disease with autonomic dysfunction [Pathak and Senard, 2006]. Ingestion of a meal may lead to abnormal postprandial cardiovascular responses and aggravation of the parkinsonian stage. The underlying mechanisms are unclear, although vasodilatory gut peptides released in response to food ingestion may be contributory [Chaudhuri *et al.* 1997]. Although caffeine is often recommended as treatment for postprandial hypotension, available data do not prove its use. Octreotide, a somatostatin analogue, has been shown to be effective, but it is expensive and must be given parenterally [Jansen and Lipsitz, 1995].

It needs to be considered that antihypotensive drugs have significant adverse effects. In a prospective study of 121 patients with symptomatic orthostatic hypotension Pathak *et al.* could demonstrate a high frequency of serious and unexpected adverse effects after the use of antihypotensive drugs [Pathak *et al.* 2005]. This strongly suggests the need for a better evaluation of the safety profile of antihypotensive drugs. Furthermore, patients need to be closely monitored during their therapy particularly when on multiple drugs.

## Supine hypertension

Orthostatic hypotension may be accompanied by supine hypertension [Goldstein *et al.* 2003]. Supine hypertension is a common feature in chronic autonomic failure. Goldstein *et al.* observed that PD and MSA patients with orthostatic hypotension had higher mean arterial pressure during supine rest than those without. Supine hypertension is linked to low baroreflex-cardiovagal gain which is quite common in patients with extrapyramidal disease [Friedrich *et al.* 2009, 2008]. Patients also exhibit lower plasma norepinephrine levels, which suggest involvement of pressor mechanisms independent of the sympathetic nervous system.

The presence of orthostatic hypotension is an independent predictor of all-cause mortality [Schatz, 2002]. Concomitant reversal of the circadian blood pressure pattern, and postprandial hypotension may contribute to the increased mortality in patients with orthostatic hypotension. Twenty-four-hour ambulatory blood pressure monitoring is the method of choice for assessment of blood pressure variability in orthostatic hypotension [Ejaz *et al.* 2007]. Recently, we observed a high prevalence of altered 24 h blood pressure profile including loss of the nocturnal blood pressure dip in PD and MSA patients [Schmidt *et al.* 2009a]. We found good correlations between orthostatic hypotension, supine hypertension and altered 24 h blood pressure profile.

Supine hypertension must be taken into consideration when treating orthostatic hypotension. Antihypotensive medication should be taken later than 5 pm. Fine-tuned nocturnal antihypertensive therapy (e.g. clonidine) maybe necessary to prevent severe nocturnal blood pressure peaks [Pathak and Senard, 2006; Shibao *et al.* 2006a]. The clonidine-induced blood pressure fall is only modest but correlates with the magnitude of residual sympathetic tone.

Supine hypertension is a common finding in patients with autonomic dysfunction; it is associated with end-organ damage and produces night-time pressure diuresis with worsening of orthostatic hypotension. During the daytime, it is best treated by avoiding the supine posture.

At night, simple measures such as raising the head of the bed by 15–20 cm can be effective, but most patients require pharmacologic treatment. Transdermal nitroglycerin (0.1–0.2 mg/h) or nifedipine (30 mg, orally) has proved to be effective [Shibao *et al.* 2006b]. Hydralazine and minoxidil are usually less effective but may be useful in a given patient. One key therapeutic concept is the hypersensitivity of these patients to depressor agents, requiring a careful titration of the doses on an individual basis. For those patients with proven residual sympathetic tone, as in MSA, central sympatholytics such as clonidine may provide an alternative [Ziemssen and Reichmann, 2007]. Repeated 24 h ambulatory blood pressure monitoring is recommended for evaluation of therapeutic efficiency [Schmidt *et al.* 2009a].

## Cardiovascular effects of antiparkinsonian drugs

The debate about antiparkinsonian drugs as cause for orthostatic hypotension has been ongoing for a long time [Ziemssen and Reichmann, 2009]. One limitation is the lack of studies investigating this cause–effect relationship. Findings from studies on levodopa have been controversial. Whilst a few studies found a reduced HR response and enhanced blood pressure drop after standing up in patients taking levodopa [Camerlingo *et al.* 1990; Sachs *et al.* 1985], others did not [Goetz *et al.* 1986; Kuroiwa *et al.* 1983; Sachs *et al.* 1985]. In a study applying 133-xenon washout technique, chronic levodopa treatment did not cause any changes in sympathetic reflex mechanisms [Andersen and Boesen, 1997]. In another study, the myocardial 6-[$^{18}$F]-fluorodopamine-derived radioactivity which reflects unchanged functional sympathetic nerve terminals [Goldstein *et al.* 2000].

The use of dopamine receptor agonists has been associated with low resting blood pressure [Quinn *et al.* 1981] and a pronounced fall in orthostatic blood pressure [Kujawa *et al.* 2000; Lewitt *et al.* 1983; Tanner *et al.* 1982; Greenacre *et al.* 1976]. In a recent study, orthostatic hypotension was frequently observed after initiation of dopamine agonist therapy in PD patients. However, the patients themselves seldom perceived it restricting, and there was also no association to the use of a specific dopamine agonist [Kujawa *et al.* 2000]. In a prospective placebo-controlled trial on selegiline, Turkka *et al.* [1997]demonstrated a slight blockade of sympathetic autonomic responses. In contrast, another study found an association of combined intake of selegiline and levodopa with orthostatic hypotension [Churchyard *et al.* 1997]. Cessation of selegiline therapy considerably diminished the fall in blood pressure during orthostasis.

## Gastrointestinal system

### *Dysphagia*

James Parkinson unambiguously portrayed advanced dysphagia in the 'shaking palsy' [Parkinson, 1817]. Dysphagia relates not only to a defect of swallowing but refers to a dysfunction of the complex motor cascade beginning prior to the swallow and ending when a bolus passes the lower oesophageal sphincter (ingestion). It is an often unrecognized complication that occurs in a majority of patients with extrapyramidal disorders. The pathophysiology of dysphagia involves in part bradykinesia and rigidity in the oral phase of swallowing, in part dysregulation of autonomic centres (i.e. nuclei of cranial nerves, oesophageal myenteric plexus). Although dysphagia is usually asymptomatic, a detailed clinical and radiological examination of patients with symptomatic dysphagia typically identifies multiple abnormalities in each phase of ingestion [Pfeiffer, 2003]. The exact prevalence of dysphagia in extrapyramidal disease is unknown, but may range from about 50–100% especially when radiological abnormalities are included [Lieberman *et al.* 1980]. The relationship between prevalence and severity of disease has received little attention. The consequences of dysphagia are usually both psychological (anxiety, reduction of food selection, social isolation) and physical (aspiration risk, anteroflexed posture, pneumonia as most common cause of death) [Ekberg *et al.* 2002]. Minimal dysphagia with a relative low risk of aspiration presents historically as isolated sialorrhoea.

There are no satisfactory therapies for dysphagia. Therefore, instead of overriding consensus for treatment, little more exists than results based on anecdotal data [Baijens and Speyer, 2009]. Further research based on randomized, controlled trials to determine the effectiveness of different therapies for dysphagia in Parkinson's disease is required.

Dopamine agonists and levodopa ameliorate some symptomatic and radiological swallowing abnormalities [Hunter *et al.* 1997]. But because

dopaminergic pathways have little impact on swallowing, dopaminergic agents have most impact on the prepharyngeal phases of ingestion, those phases under the greatest volitional control. Anticholinergics can be used to reduce the production of saliva in dysphagia but may evoke potential side-effects such as constipation, urinary retention, memory problems and even hallucinations. Positive effects of salivary gland botulinumtoxin injections have been demonstrated as well [Pal *et al.* 2000], but these may be compromised by possible complications (i.e. dry mouth, possible injection errors, muscle weakness). By experience, speech therapy, physical aid (chewing gum to increase the swallowing frequency) and pharmacotherapy to optimize motor function play an important therapeutic role [Logemann *et al.* 2008]. Studies on nonpharmacological interventions of swallowing training as dietary alternatives or modification of food consistency are extremely rare [Baijens and Speyer, 2009].

Dysphagia specialists can also introduce various techniques from a collection of compensatory strategies. MSA patients presenting with severe dysphagia may require feeding via a nasogastric tube or even percutaneous endoscopic gastrostomy.

### *Gastric dysfunction*

Impairment of gastric motility has been reported to be present in 70% of PD patients [Djaldetti *et al.* 1996]. Gastric motor dysfunction (delayed gastric emptying) is usually associated with early satiety, anorexia, abdominal fullness (bloated feeling?), nausea and vomiting [Pfeiffer, 2003]. A growing body of evidence indicates that gastrointestinal symptoms primarily reflect direct involvement of the gastrointestinal tract in the neurodegenerative process (Lewy bodies in autonomic plexus, loss of autonomic neurons) [Wakabayashi *et al.* 1993]. Treatment of gastric dysfunction is important, not only because of its symptomatology, but also because it may affect drug absorption and consequently lead to manifestation of motor symptoms. Disturbed gastric motility may elicit at least partly the on–off phenomena [Sage and Mark, 1994]. On the other side, dopamine-mimetic agents inhibit gastric emptying thereby further exacerbating gastric dysfunction [Robertson *et al.* 1992].

Nonpharmacological treatment includes a diet consisting of small but frequent low-fat meals [Friedenberg and Parkman, 2007]. Cessation of anticholinergic medication may also be beneficial in the management of gastroparesis. Erythromycin is the most potent prokinetic drug when given intravenously in the acute setting and is therefore indicated for the initial management of hospitalized patients with severe gastroparesis [Friedenberg and Parkman, 2006]. Limitations of treatment with erythromycin include its potential to induce abdominal cramps and nausea, and to retard small-intestinal transit as well as its antibiotic effects. Gastroparesis can be efficiently treated by cisapride resulting in long-term symptomatic relief [Jost *et al.* 1997]. Furthermore, it accelerates intestinal transit. Cisapride has recently been withdrawn from many markets owing to its potential to induce cardiac arrhythmias. Domperidone has antiemetic and prokinetic effects, although central nervous system reactions are uncommon owing to its inability to penetrate the blood–brain barrier [Barone, 1999]. The prokinetic effects of domperidone seem to be comparable in magnitude to those of metoclopramide. Domperidone speeds up the emptying of the stomach, facilitates resorption of levopopa in the small intestine, and hence increases levopoda plasma levels. Domperidone can also be used as adjunct to levodopa therapy which reduces side-effects such as nausea [Lertxundi *et al.* 2008]. In a small percentage of patients the insertion of a gastrostomy or jejunostomy feeding tube may be indicated for administration of dopaminergic drugs and optimal nutritional care [Rabine and Barnett, 2001]. Advances in understanding the normal gastric electromechanical function and its abnormalities has led to the development of gastric electrical stimulators, analogous to devices that stimulate other dysfunctional organs [Maranki and Parkman, 2007].

### *Intestinal dysfunction/constipation*

Since Parkinson's first description, constipation or decreased bowel movement frequency due to colonic dysmotility is one of the most common problems among PD patients even before diagnosis of the illness [Sakakibara *et al.* 2008]. Data from the Honolulu Heart Program study suggest that diminished bowel movements frequency may actually constitute a risk factor of PD development [Abbott *et al.* 2001]. Constipation is closely linked to slow colonic transit time, which continues to lengthen during the disease. Constipation can cause megacolon, pseudo-obstruction, volvulus, ileus or perforation.

The pathophysiology of reduced colon transit time may include dysfunction of central autonomic centres (eg. Barrington's nucleus) and peripheral changes in the myenteric and submucosal autonomic plexus itself [Benarroch *et al.* 2006; Pfeiffer, 2003]. The treatment of slow-transit constipation can be difficult and frustrating. First, an increased fibre and fluid intake is recommended. If dietary measures do not relief constipation sufficiently, an osmotic laxative such as lactulose or sorbitol may be additionally administered. More recently, the effectiveness of polyethylene glycol electrolyte-balanced solutions has been demonstrated in PD patients [Zangaglia *et al.* 2007]. This colon-cleansing agent is routinely used in large amounts in preparation to colonoscopy. Regular administration of small doses are considered safe for treating constipation in PD. Patients often make use of effective but irritant laxatives, such as senna-containing compounds. These laxatives are not recommended for daily use since they may damage the myenteric plexus. The value of prokinetic agents in the treatment of constipation is uncertain [Pfeiffer, 2003]. Discontinuing anticholinergic agents may increase bowel motility. Increasing physical activity can also be helpful.

### *Anorectal dysfunction*

The defecation process can also be disturbed. Anorectal dysfunction, characterized by excessive straining with concomitant sensation of incomplete evacuation and sometimes of pain, is the most prevalent form of bowel dysfunction [Stocchi *et al.* 2000; Edwards *et al.* 1991]. Reduced basal sphincter pressure and difficulty maintaining sphincter pressure have been documented by anorectal manometry. Though some patients exhibit more distinctive abnormalities including unusual phaseal sphincter contractions or paradoxical hypercontractile responses of the external sphincter [Ashraf *et al.* 1995]. These abnormalities may predispose to a so-called anismus which describes sporadic contractions of the anal sphincter in the sense of dystonia.

The treatment of defecation dysfunction is complicated because common laxatives do not improve the coordination of the anorectal muscles but commonly worsen symptoms. Laxatives lead to preterm arrival of stool in rectum which may increase rectal retention time und thus water reabsorption. Dopaminergic medication or apomorphine injections may individually improve anorectal function [Ashraf *et al.* 1995]. Injection of botulinum toxin into the puborectalis muscle is effectively in treating outlet obstruction-type dysfunction [Albanese *et al.* 2003]. Behavioural techniques such as defecation training and biofeedback measures have been successfully employed in the treatment of outlet obstruction constipation [McKee *et al.* 1999].

## Urological system

Urogenital dysfunction is present in up to 93% of PD patients with frequency, urgency and urge incontinence being predominant symptoms [Micieli *et al.* 2003; Lemack *et al.* 2000]. Voiding dysfunctions play an important social role among PD patients. Frequent voiding considerably impairs nocturnal sleep and quality of life. Urogenital dysfunction can occur in consequence of medications or primary neurodegenerative disease, independently of extrapyramidal disease. Like PD patients MSA patients develop early symptoms of urinary and erectile dysfunction [Papatsoris *et al.* 2008; Kirchhof *et al.* 2003]. Lower urinary tract infections are a major cause of morbidity and mortality in MSA [Papatsoris *et al.* 2008]. More than 50% of MSA patients suffer from recurrent infections and a significant number (approximately 25%) die of subsequent complications.

Urogenital symptoms are usually based on a multitude of central and peripheral nervous abnormalities which are sometimes superimposed on previous local pathological conditions such as benign prostatic hyperplasia and perineal laxity. Missclassification of urogenital autonomic dysfunction as benign prostatic hyperplasia has been reported which may increase the risk of unnecessary urological surgery [Chandiramani *et al.* 1997]. Therapy should be implemented in close cooperation with a neuro-urologist. The primary goal of the therapy is to control voiding and to avoid incontinence.

Detrusor hyperreflexia is a cystometric finding characterized by the presence of involuntary detrusor contractions in response to bladder filling which are often associated with irritative symptoms [Andersen, 1985]. Voiding dysfunction results from the loss of inhibitory effect that basal ganglia exert on the pontine micturation centre. Irritative symptoms are responsive to anticholinergic drugs which decrease detrusor activity. Oxybutinin and tolterodine are among the more frequently used anticholinergic drugs. Side effects include hesitancy, week urinary

stream, dry mouth, impaired visual accommodation, constipation and aggravation of glaucoma. Botulinum toxin A intradetrusor injections constitute a safe, conservative, reversible and short-term effective (6–12 months) alternative after failure of anticholinergic therapy for overactive bladder and its clinical consequences [Karsenty *et al.* 2007]. The efficacy of the first injection appears to be maintained at subsequent injections.

Detrusor areflexia is a cystometrographic finding which is characterized by decreased sensation during filling and increased bladder capacity. Clinical symptoms are hesitancy and weak urinary stream. Detrusor areflexia is rare and mostly a consequence of anticholinergic drugs [Stocchi *et al.* 1993]. Dopaminergic medication has no consistent effects on detrusor activity.

Patients with extrapyramidal disease may also present with dysfunctional intravesicle mechanisms. Most frequently, a sphincter bradykinesia consisting of delayed relaxation of the striated urethral sphincter can be found [Bonnet *et al.* 1997]. In addition, detrusor sphincter dyssynergia is less often reported by patients with extrapyramidal disease [Sakakibara *et al.* 2001]. Before instituting therapeutic measures such as intermittent or permanent catheterization structural causes of obstruction have to be ruled out.

Patients with MSA frequently suffer from poor bladder compliance and sphincter insufficiency [Sakakibara *et al.* 2001, 2000] which may evoke episodes of incontinence, including both overflow and stress incontinence. Intermittent catheterization with or without concomitant administration of anticholinergics may be the initial treatment [Papatsoris *et al.* 2008]. Progressing motor dysfunction over time may render permanent indwelling catheterization or suprapubic cystotomy necessary. The urogenital criteria for differential diagnosis of MSA are [Chandiramani *et al.* 1997]: (1) urinary symptoms preceding or concurring with parkinsonism; (2) urinary incontinence and PD; (3) a significant post-void residual urine volume; (4) erectile failure preceding or concurring with parkinsonism; and (5) worsened bladder control after urological surgery. Patients with parkinsonism who report urogenital symptoms should be offered medical management rather than urological surgery [Berger *et al.* 1987]. As yet there are no biomarkers which may predict successful surgical outcome. Urologists should be aware of the necessity to rule out MSA prior to surgery.

## Sexual function

Like urological dysfunction, there is a higher incidence of impaired sexual function in patients with extrapyramidal disease than in the general population [Meco *et al.* 2008; Yu *et al.* 2004]. Patients usually complain about impaired libido, erection and/or ejaculation or compromised sex life.

Erectile dysfunction is nearly twice as frequent in men with Parkinson's disease as in controls [Hobson *et al.* 2003]. PD patients are less satisfied with their sexual relationships and with their partners, and are more depressed when compared with controls [Brown *et al.* 1978]. Women reported difficulties with arousal (87.5%), with experience of orgasm (75%), with low sexual desire (47%), and with sexual dissatisfaction (38%). Men reported erectile dysfunction (68%), sexual dissatisfaction (65%), premature ejaculation (41%), and difficulties in experiencing an orgasm (40%). Sexual dysfunction is frequently recognized as manifestation of autonomic failure in PD. Dysautonomia has long been perceived as late manifestation of PD. Based on that assumption dysautonomia assisted in differentiating PD from other parkinsonian syndromes in which dysautonomia typically is an early clinical feature. Indeed, sexual dysfunction is invariably present in patients with MSA [Kaufmann and Biaggioni, 2003]. In men, erectile dysfunction is the most frequent primary symptom in MSA. About 50% of female MSA patients report reduced genital sensitivity compared with only 4% of female PD patients [Oertel *et al.* 2003]. The occurrence of genital insensitivity in female and erectile dysfunction in male MSA patients was closely related to disease onset. With the understanding that dysautonomia can occur in any stage of PD it is ineligible for differential diagnosis [Jost, 2003].

Several studies have reported varying increments in sexual desire (1–50%) associated with dopaminergic therapy [Yu *et al.* 2004; Kanovsky *et al.* 2002]. Dopaminergic therapy may affect sexual behaviour by direct stimulation of the D2 receptor in the medial preoptic area. Alternatively, sexual stimulation by dopaminergic drugs may be achieved through inhibition of prolactin secretion and increase of plasma oxytocin levels. The latter produces erectogenic effects in

the lumbosacral spinal cord. Dopaminergic stimulation may lead to the resumption of sexual activity and hypersexuality in some patients [Meco *et al.* 2008]. In a patient with normal erectile function subcutaneous administration of apomorphine, a D2-like receptor selective dopaminergic agonist, resulted in penis erection within 10 min. Erection lasted up to 60 min which caused physical stress and increased libido [O'Sullivan, 2002]. Similarly, ropinirole (3 mg administered three times daily) caused an involuntary erection within 30 min of administration in a patient without sexual dysfunction. The erection lasted 10–15 min and caused physical and psychological discomfort. The number of involuntary erections decreased when a lower dosage (1 mg) was administered, and ceased when administration was discontinued [Fine and Lang, 1999]. Findings of an open, 6-month follow-up study by Pohanka *et al.* [2004] revealed that pergolide mesylate (3 mg daily) improved sexual function in young men suffering from PD. Sildenafil citrate administered at a dose of 50 mg improved erectile dysfunction in 10 men with PD [Zesiewicz *et al.* 2000]. Raffaele *et al.* evaluated the efficacy of sildenafil in depressed men with PD: improved erection was reported by 85% of patients, while an improvement in depressive symptoms was observed in 75% [Raffaele *et al.* 2002]. However, it may unmask or exacerbate hypotension in MSA [Hussain *et al.* 2001]. As PD may be diagnostically difficult to distinguish from MSA, especially in the early stages, we recommend measurement of lying and standing blood pressure before prescribing sildenafil to men with parkinsonism. Furthermore, such patients should be made aware of seeking medical advice if they develop symptoms on treatment suggestive of orthostatic hypotension.

## Sudomotor system

Sweating (i.e. sudomotor) abnormalities have long been described in PD. More recently, it has been reported that sweating abnormalities may antedate their initial diagnosis. Research findings indicate that the severity of sweating abnormalities increases as motor function declines [Yoshioka *et al.* 2003]. Both hypohidrosis as well as hyperhidrosis have been described. Hypohidrosis is most common at lower extremities whilst the upper trunk, neck and face are rather affected by hyperhidrosis [Schestatsky *et al.* 2006]. Head and neck hyperhidrosis could be a compensatory response to impaired sweating in other body regions. Because this type of hyperhidrosis may be an appropriate thermoregulatory compensatory response to appendicular sudomotor dysfunction, it should not be specifically treated. Hyperhidrosis may occur on a paroxysmal basis with the paroxysms being triggered by OFF periods [Pursiainen *et al.* 2007]. This episodic hyperhidrosis may improve with optimized dopaminergic therapy which may be achieved by adjunct therapy with either a second dopamine agonist, a COMT inhibitor or betablocker (eg. propanolol) or by a closer spacing of levodopa dose. Administration of anticholinergics such as 50 mg pirenzepine twice daily or 100 mg sage extract three to four times daily may efficiently treat hyperhidrosis [Swinn *et al.* 2003]. Topical externa of aluminium basis or botolinumtoxin injections can be applied in the rare cases of focal hyperhidrosis [Naumann and Jost, 2004].

## Conclusions

It should be reiterated that extrapyramidal disorders frequently affect the autonomic nervous system. As early as 1913 Lewy described that 'The dynamic character of the clinical picture of an extrapyramidal disease must result from other participating (nonmotor) systems we do not know enough about' [Lewy, 1913]. Therefore diagnosis and therapy of these often neglected autonomic symptoms should become routine in clinical practice!

## Conflict of interest statement

None declared.

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