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Emergencies and critical issues in Parkinson's disease

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ABSTRACT

Complications from Parkinson's disease may develop over the disease course, sometimes unexpectedly, and require prompt or even urgent medical intervention. The most common are associated with aggravation of motor symptoms; serious non-motor complications, such as psychosis, orthostatic hypotension or sleep attacks, also occur. Here we review such complications, their clinical presentation, precipitating factors and management, including those related to using device-aided therapies. Early recognition and prompt attention to these critical situations is challenging, even for the Parkinson's disease specialist, but is essential to prevent serious problems.

INTRODUCTION

People with Parkinson's disease may develop acute and subacute complications that are serious or even life-threatening, and require prompt medical attention.[1] Some emergencies are intrinsic to the disease, while others result from an interaction of various medical and surgical treatments with the disease process. These conditions often present a diagnostic and management challenge.

Emergencies may result from motor deterioration, or there may be non-motor issues such as neuropsychiatric problems, autonomic dysfunction syndromes and sleep disorders. Occasionally patients need to be hospitalised and to receive multidisciplinary care.[2] Boxes 1 and 2 provide illustrative examples, drawn from the literature and our experience.

We also discuss complications relating to device-aided therapies, such as deep-brain stimulation, levodopa-carbidopa intestinal gel and subcutaneous apomorphine, since these are now frequently used in advanced Parkinson's disease and can have potentially serious complications. We also make recommendations to help clinicians minimise or prevent complications, especially in the inpatient setting.

EMERGENCIES WITH PROMINENT AGGRAVATION OF PARKINSONISM OR DYSKINESIAS

Severe parkinsonism (hypokinesia) and generalised hyperkinesia are common in people with Parkinson's disease. These disabling motor syndromes usually develop in advanced disease, manifesting as prominent fluctuations associated with chronic levodopa therapy.[3] Motor complications are usually managed initially in an outpatient setting but if severe may need hospitalisation. Rare cases can progress to fever and rhabdomyolysis, resembling neuroleptic malignant syndrome, and requiring intensive care unit treatment.

Severe levodopa-related motor complications

Recurrent offs

Almost everyone taking levodopa may develop response fluctuations.[4] They typically appear after the so-called 'honeymoon' period, characterised by a favourable and stable levodopa response.[5] Motor fluctuations comprise recurrent episodes of parkinsonism (off periods) of variable intensity that occur at different times in relation to levodopa intake (wearing off, delayed-on, no-on, unpredictable off).[3]

In some patients, especially those with younger onset or those taking higher doses of levodopa, motor fluctuations become severe, causing great discomfort.[3] Severe off-related parkinsonism can manifest with a wide range of symptoms, especially severe tremor and unmanageable freezing of gait. These episodes are frequently associated with pain, profuse sweating and tachycardia, abdominal discomfort, and also psychiatric manifestations, particularly depression and anxiety.[6]

Box 1 Illustrative case of parkinsonism-hyperpyrexia syndrome

A 73-year-old man with a 15-year history of Parkinson's disease was admitted for neurosurgical evacuation of traumatic subdural haematoma. His parkinsonism had deteriorated in the last 3 months despite high daily levodopa dosage (1200 mg). During the postoperative period, his bradykinesia and rigidity markedly worsened. There was no clear improvement despite increasing the levodopa in combination with dopamine agonists in several presentations (oral, transdermal and subcutaneous). He became confused, febrile and diaphoretic. On examination, he had marked generalised rigidity and bradykinesia. CT scan of head was normal. Other factors that may aggravate parkinsonism, such as addition of dopaminergic blockers, and concurrent medical conditions, were ruled out. Blood tests showed high muscle enzyme levels and markers of acute renal failure. Response to dopaminergic therapy remained minimal. He later developed shortness of breath and tachycardia. Pulmonary embolism was diagnosed and he was admitted to the intensive care unit. Levodopa was administered via a nasogastric tube and intense physiotherapy implemented with gradual improvement of his health status although daily functioning was still significantly impaired despite continuous dopaminergic therapy.

Learning points: Risk (advanced Parkinson's disease taking high dose of levodopa) and contributor factors (recent surgery and hospitalisation) to develop parkinsonism-hyperpyrexia syndrome; benefit of nasogastric levodopa administration in cases with an inappropriate oral intake; the relevance of paying attention to systemic complications.

Box 2 Illustrative case of acute psychosis

An 80-year-old woman with Parkinson's disease was brought by her caregiver to the hospital emergency room because of marked agitation and paranoid ideation. She had physically attacked a staff member at the nursing home where she had been recently placed. One year earlier she developed visual hallucinations, initially well controlled with quetiapine (75 mg two times per day). In the last 6 months she had developed frequent delusions with loss of insight. On admission to the Neurology ward she was taking 300 mg per day of levodopa and quetiapine (125 mg per day). Her cognitive state was normal. Other medical conditions known to cause acute psychosis were ruled out. Several treatment changes were tried. First, levodopa dose was halved without any significant motor worsening or improvement in hallucinations or delusions. In consequence, quetiapine was switched to clozapine (12.5 mg per day), prompting improvement in psychiatric symptoms. In the end, levodopa was raised back to 300 mg a day and clozapine was maintained. A few months later she had developed cognitive decline and rivastigmine was added.

Learning points: Psychosis exacerbation after nursing home placement; loss of insight and delusions as severity markers; before adding antipsychotic therapy for psychosis consider dopaminergic drug reduction, especially in advanced disease stages; after acute episode resolution check cognitive status.

The treatment aims to reduce off time and severity by providing a more constant delivery of dopaminergic drug to the brain.[6] By the time these problems develop, patients are taking multiple doses of levodopa and most have tried adjunctive treatments aiming to prolong levodopa effect: such adjuvant treatments include dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, and monoamine oxidase B (MAO) inhibitors. Changing the levodopa dose through the day and adjusting the adjuvant medications can minimise the fluctuations and make them more predictable.[5] However, about 10% of patients have severe medically refractory fluctuations; such patients require referral to specialised centres for consideration of device-aided therapies.[3] However, age, cognitive status and the presence of psychotic symptoms frequently limit the use of these therapies.[7]

Dyskinesias

Involuntary movements (dyskinesias) can develop at different times in relation to the antiparkinsonian effect of levodopa (peak-dose and diphasic dyskinesia, or off-period painful dystonia).[3] Although levodopa-induced dyskinesias are usually mild and focal in distribution, they can sometimes become generalised and interfere with sitting, walking and basic activities of daily living. This is more common in people with young-onset Parkinson's disease.[3] Patients then need urgent interventions to prevent consequences, such as falls and other injuries (ie, bone fractures). Moreover, severe dyskinesias, both peak-dose or diphasic, can occur at the end of the day in people taking slow-release formulations of oral levodopa, or in those receiving levodopa-carbidopa intestinal gel infusions.[8]

Treatment of dyskinesia is based on adjusting dopaminergic treatments. Peak-dose dyskinesias usually improve with redistributing the total daily levodopa intake into more frequent but smaller doses. Some patients need a lower total dose of levodopa (or lower dose of adjunctive therapies such as dopamine agonists, COMT inhibitors or MAO inhibitors). If these measures fail, then it is worth considering amantadine (300–400 mg daily).[7]

Managing diphasic dyskinesias is a major clinical challenge in advanced Parkinson's disease.[6] Modifying treatment, as would be done for peak-dose dyskinesias, may in fact worsen diphasic dyskinesias; sometimes the only suitable alternative is an intermittent 'rescue' subcutaneous injection of apomorphine immediately before an on/off state transition.[6 9] In patients whose dyskinesias do not respond, it is worth considering one

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Table 1 Precipitant factors of severe off and the parkinsonism-hyperpyrexia syndrome

Dopaminergic treatment related	Non-dopaminergic treatment related
Abrupt withdrawal or medication switch Decrease of absorption: ► Enteral and parenteral nutrition with high protein diet ► Gastrointestinal problems (severe constipation, paralytic ileus) Dosage reduction: ► Loss of compliance ► Psychiatric problems (confusion, hallucinations) ► Severe dyskinesia ► Postoperative period Addition of dopaminergic blocker	Concurrent conditions: ► Infection ► Trauma ► Stress ► Dehydration ► Excessively hot weather

of the available continuous dopaminergic treatments or deep-brain stimulation.[9]

These strategies for managing wearing off and unpredictable on/off fluctuations also apply to off-period dystonia. Baclofen or injecting botulinum toxin into dystonic muscles can occasionally help.[10]

Parkinsonism-hyperpyrexia syndrome

Some patients develop an acute 'akinetic attack' (known as parkinsonism-hyperpyrexia syndrome), a severe complication with an incidence of 0.3% and mortality of 4%.[11 12] It may follow an abrupt change in dopaminergic medication although there are various other possible precipitant factors (table 1).

Clinical picture

This syndrome was first noted in people with advanced Parkinson's disease undergoing 'drug holidays' to try to limit their levodopa-induced motor and neuropsychiatric complications.[12] Patients deteriorated into an akinetic 'off' state, usually over a few days. The syndrome may also follow changes in dopaminergic treatment or be provoked by trauma, surgery, and pulmonary, gastrointestinal and urinary tract infections; although sometimes there is no apparent trigger.[11] In severe cases, patients do not respond to dopaminergic rescue medications, with their parkinsonism deteriorating rapidly and becoming progressively more immobile and rigid.

On examination, patients may be confused with delirium, prominent global slowness and generalised muscle rigidity. They may develop hyperthermia and elevated serum muscle enzymes, following muscle damage from marked rigidity. Some patients develop dysautonomic features, such as tachycardia, unstable blood pressure and diaphoresis, resembling the clinical picture of neuroleptic malignant syndrome.[13]

Systemic complications may develop as the akinesia rapidly progresses, including aspiration pneumonia from decreased level of consciousness and rigidity; acute renal failure from rhabdomyolysis and dehydration; and thrombotic events such as deep vein thrombosis, pulmonary thromboembolism or (in severe cases) disseminated intravascular coagulation (box 1).

How to manage?

Early diagnosis is essential. Besides searching for and correcting the underlying cause, levodopa is the core of its management.[11 14] If the syndrome was provoked by a decreased dose of dopaminergic treatment, the previous regimen should be immediately reinstated, and the oral levodopa dose gradually escalated. In patients with swallowing problems, a nasogastric tube can facilitate giving dopaminergic treatment. If increasing the levodopa dose fails, it is worth trying apomorphine (intermittent injections or continuous infusion), transdermal rotigotine or intravenous amantadine sulfate (only available in Germany, Austria and Hungary).[13] The most refractory cases may be considered for nasogastric levodopa-carbidopa gel infusion with titrated dosing. Other treatments such as oral dantrolene sodium and oral bromocriptine are recommended but have no firm evidence of efficacy.[12] Pulsed corticosteroid therapy (1 g daily of methylprednisolone until amelioration of symptoms) may help but again with only limited evidence of its effectiveness.[15]

Some patients need intensive care unit admission, for close monitoring of vital signs and supportive measures such as antipyretic treatment, fluid and electrolyte replacement, and prophylactic anticoagulants.[2] Patients need routine checking of serum muscle enzymes, renal function (to identify deterioration) and clotting function (figure 1).

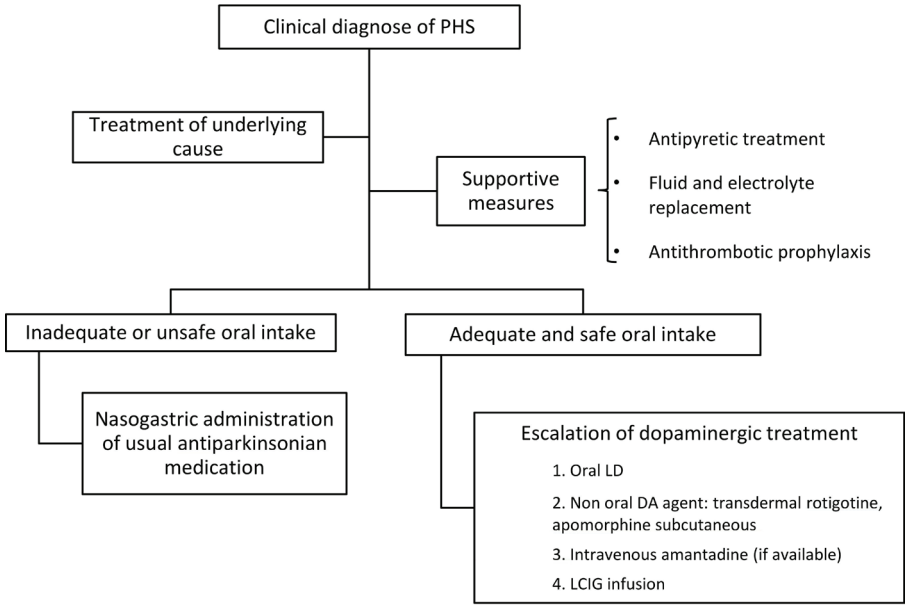
The prognosis is usually good with early treatment, although many patients do not return to their previous baseline level of function.[12]

Dyskinesia-hyperpyrexia syndrome

Levodopa-induced dyskinesias can be severe and occasionally even life-threatening, presenting as a dyskinetic storm (also known as dyskinesia-hyperpyrexia syndrome).[13]

Clinical picture

Patients typically present with prolonged episodes of generalised and exhausting dyskinetic movements that eventually cause motor collapse with consequent dehydration and rhabdomyolysis.[16 17]



PHS: parkinsonism-hyperpyrexia syndrome, LCIG: levodopa/carbidopa intestinal gel, DA: dopamine agonist, LD: levodopa

Figure 1 Management of parkinsonism-hyperpyrexia syndrome. DA, dopamine agonist; LCIG, levodopa/carbidopa intestinal gel; LD, levodopa.; PHS, parkinsonism-hyperpyrexia syndrome

This condition shares features with parkinsonism-hyperpyrexia syndrome: acute or subacute presentation, external trigger factors (infection and trauma) and systemic impairment (hyperthermia and rhabdomyolysis).[2] Some patients may be refractory to treatment (limited response to reducing the dopaminergic medication or adding amantadine) but this is clearly less important than for parkinsonism-hyperpyrexia syndrome. Reducing dopaminergic drugs almost always improves dyskinesias in a short period of time.[6 17]

How to manage?

Besides promptly reducing the dopaminergic medication, patients may need general measures such as rehydration and electrolyte monitoring and repletion. In extreme cases, they may need sedation with propofol. Deep-brain stimulation may be a feasible long-term treatment.[13]

Serotonin syndrome

Serotonin syndrome is a rare but preventable adverse effect of serotonergic agonist treatment; it culminates in a hyperserotonergic status due to overstimulation of postsynaptic serotonin (5-HT or 5- hydroxytryptamine) receptor in the central nervous system.[18] The syndrome can be potentially induced by drugs frequently used in Parkinson's disease treatment, including MAO inhibitors (selegiline, rasagiline and safinamide), selective-serotonin reuptake inhibitors, tricyclic antidepressants and opiates.[4] Because patients with Parkinson's disease often have pain and depression, they may be taking a combination of all of these treatments, putting them at an increased risk to develop the syndrome.

Clinical picture

Although serotonin syndrome shares many features with parkinsonism-hyperpyrexia syndrome and neuroleptic malignant-like syndrome (mental status decline and autonomic dysfunction; table 2), its onset is more rapid after starting or increasing the medication, usually within 6–12 hours.[2] Its clinical manifestations vary but in addition to agitation and confusion there are four features that may help with the diagnosis:

Table 2 Parkinsonism-hyperpyrexia and serotonin syndromes

Parkinsonism-hyperpyrexia syndrome	Serotonin syndrome
Muscle rigidity, prominent akinesia	Tremor, myoclonus, akathisia, hypertonicity
Altered mental status Hyperthermia Rhabdomyolysis	
Trigger factors	
Infection, trauma, medication changes	Drug combinations: MAO inhibitor, SSRI, tricyclic antidepressant, opioids
Treatment	
Escalating dopaminergic treatment	Stopping the causative drug
Supportive intensive care management	

MAO, monoamine oxidase B; SSRI, selective-serotonin reuptake inhibitor.

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mixture of movement disorders (akathisia, tremor and myoclonus), hyperreflexia, mydriasis and diarrhoea.[18]

How to manage?

The cornerstone of treatment is to identify and withhold all drugs that could contribute to the hyperserotonergic state. Prompt and appropriate supportive care can be important for recovery, and adding non-selective 5-HT receptor antagonists (cyproheptadine and methysergide) may help.[18]

SELECTED NON-MOTOR EMERGENCIES

Neuropsychiatric complications

Neuropsychiatric disorders are common in Parkinson's disease. They can be life-threatening and invariably are distressing for patients and caregivers. Psychosis, anxiety, panic attacks, depression, impulse-control disorders and dopamine-dysregulation syndrome are among the most disabling neuropsychiatric complications.

Acute psychosis

Psychotic symptoms occur in up to 30% of patients with Parkinson's disease who take long-term dopaminergic treatment throughout the disease course; their occurrence suggests a poor prognosis and high mortality.[19] Psychotic symptoms are well known to be an integral part of Parkinson's disease, frequently triggered or aggravated by antiparkinsonian medications and a predictor of imminent cognitive decline.[20]

Hallucinations (mainly visual with well-formed images and rarely auditory) and delusions (commonly paranoid, implying negative beliefs, especially towards relatives) are the hallmark of Parkinson's disease psychosis.[20] Loss of insight, particularly when having delusions, is very stressful for caregivers, and increases the likelihood of nursing home placement. In addition, hospitalised patients with Parkinson's disease often develop other psychiatric symptoms such as confusion/delirium, typically accompanied by a fluctuating level of attention, disorganised speech and behavioural changes.[19]

Dopaminergic treatment, advanced age, visual problems and concomitant dementia are important factors that contribute to psychosis in Parkinson's disease. Psychotic symptoms may appear in relation to underlying systemic conditions such as infection, toxic-metabolic derangements, surgery and other neurological disorders (ie, subdural haematoma related to falls). Changes in antiparkinsonian drugs frequently trigger psychotic symptoms; importantly, drugs such as antidepressants and painkillers can also trigger or aggravate these symptoms.

Psychosis usually presents gradually, allowing for gradual implementation of treatment changes (reduction in dopaminergic medication, and/or addition of antipsychotic drug). However, sometimes psychosis evolves subacutely with prominent agitation and challenging behaviour constituting a serious psychiatric emergency.

In the most severe cases, when the patient's physical integrity is compromised, patients need acute psychiatric admission. The management includes intensive antipsychotic treatment, such as bucodispersable risperidone or intramuscular aripiprazole, although worsening of parkinsonism must be expected. Benzodiazepines can help if anxiety dominates the clinical picture. Containment measures are a last resort.[21]

In addition to reviewing medication changes, it is important to exclude external precipitant factors. Patients with suspected urinary tract infection or pneumonia require urine analysis and chest X-ray. It is important to try to reduce antiparkinsonian medication. Drug changes must be implemented cautiously and gradually, as motor symptoms may deteriorate significantly. A common strategy is first to reduce anticholinergic drugs, then MAO inhibitors, amantadine, dopamine agonist, COMT inhibitors and eventually levodopa, but the order of dose reduction or withdrawal may need to be individualised.[22] It is also important to minimise polypharmacy, if possible reducing mainly tricyclic antidepressants, opioids and dopaminergic drugs.

If significant psychotic symptoms persist, and drug reduction is not advisable or poorly tolerated, it is worth considering an atypical antipsychotic drug (box 2). Typical antipsychotics should be avoided as they can precipitate a significant deterioration of motor symptoms, and a neuroleptic malignant syndrome.[4] Clozapine and quetiapine are the most frequently used antipsychotics for treating psychotic symptoms in Parkinson's disease; both improve psychosis without motor worsening. Pimavanserin, a selective-serotonin inverse agonist, has recently been approved by the Food and Drug Administration (FDA) for treating psychosis in Parkinson's disease but there is only limited experience with this drug.[23 24]

In routine clinical practice, quetiapine is often the first-tried drug, owing to its easy dosing and low rates of adverse events. Its most common adverse effects are excessive sleepiness, orthostatic hypotension and metabolic syndrome. In severe cases, and if symptoms persist despite quetiapine dose exceeding 200 mg/day, clinicians should consider clozapine (12.5–50 mg) and pimavanserin, if available. Clozapine's adverse effects include sedation, drooling and orthostatic hypotension; it occasionally causes neutropenia, and so requires intensive blood monitoring, its main drawback.[25]

Cholinesterase inhibitors (donepezil and rivastigmine) were shown to reduce Parkinson's disease hallucinations and ziprasidone was effective for psychosis in Parkinson's disease in two small studies (open-label and a case series), but an exacerbation of parkinsonism can be expected.[22]

Impulse-control disorders and dopamine-dysregulation syndrome

Impulse-control disorders are a sort of behavioural addiction. Patients do not often report them because of embarrassment or cultural barriers. They include pathological gambling, compulsive shopping, abnormal sexual behaviours or binge eating.[26] Patients with this disorder are compelled to repeat these actions excessively in ways that can be dangerous for themselves and others, frequently causing devastating economic, legal and personal repercussions.

These symptoms are a frequent adverse effect of dopamine-replacement therapy. A recent study found a cumulative incidence of impulse-control disorders in 46% patients taking dopamine agonists; the association between this drug and impulse-control disorders relates to both dose and treatment duration.[27] Since its treatment is challenging, minimising the use of dopamine agonists is the best approach to lessen the problem, especially in those people at particularly high risk for developing impulse-control disorders, such young men with histories of obsessive-compulsive disorder, impulsive and addictive personality traits.[28]

Reducing dopamine agonists is the first (and usually effective) treatment. In refractory cases, adding an atypical antipsychotic, such as quetiapine, sometimes helps this reduction.[26] Deep-brain stimulation of the subthalamic nucleus[29] and levodopa carbidopa intestinal gel[30] can help by allowing dopaminergic dosage reduction.

Rapid reduction or suppression of dopamine agonists may lead to a serious condition known as *dopamine agonist withdrawal syndrome*.[31] Its clinical picture resembles a psychostimulant withdrawal syndrome, with combined psychiatric symptoms (panic attacks, depression, agitation and drug craving), autonomic features (diaphoresis, orthostatic hypotension) and motor worsening due to the reduction in dopaminergic therapy. Besides the prior diagnosis of impulse-control disorders, other risk factors are a high baseline dose of dopamine agonist and a high cumulative drug exposure. Other dopaminergic drugs, antidepressants or benzodiazepines typically do not help.[32]

A less frequent psychiatric complication related to levodopa is 'dopamine-dysregulation syndrome'. It comprises a levodopa dependence syndrome and involves all the typical symptoms of craving, with impulsivity, compulsivity and mood changes.[33] Its prevalence is probably underestimated because less severe cases are rarely reported.[6] It can coexist with impulse-control disorder and should be suspected when patients indiscriminately increase their levodopa dose without medical authorisation and exceed the required dose to restore their motor functionality. Patients may increase their levodopa dose to avoid unpleasant feelings, typically non-motor symptoms related to off episodes.[33]

The management of dopamine-dysregulation syndrome typically involves gradually reducing the levodopa and immediately withdrawing 'booster' doses of medications, such as apomorphine subcutaneous boluses and rapid-acting levodopa formulations. Deep-brain stimulation may help to facilitate dose reduction of levodopa.[26]

Dysautonomic complications

Complications related to autonomic dysfunction that may require prompt medical intervention include symptomatic orthostatic hypotension and gastrointestinal tract complications, such as dysphagia and intestinal pseudobstruction.

Symptomatic orthostatic hypotension

Orthostatic hypotension can result from both neurogenic (failure of the autonomic nervous system from postganglionic sympathetic nerves) and non-neurogenic disorders (dehydration, dopaminergic and antihypertensive drugs, and cardiac dysfunction such as arrhythmia). Neurogenic orthostatic hypotension in Parkinson's disease results from a lack of the normal compensatory norepinephrine released from sympathetic postganglionic nerves that causes vasoconstriction and maintains blood pressure in the standing position. In Parkinson's disease this compensatory mechanism is attenuated or absent.[34]

Orthostatic hypotension causes symptoms in about 10% of cases.[35] Patients usually describe lightheadedness with blurry vision on standing or walking. Concentration difficulties, postprandial head/neck discomfort, and even a frozen posture akin to a levodopa-related off episode may also occur.[35] In the most severe cases, typically when the blood pressure drops abruptly, patients may lose consciousness. Such cases require exclusion of anaemia or an underlying cardiac disorder.

Syncope caused by orthostatic hypotension can have serious consequences, including falls and injuries.[36] Identifying the drug that might be contributing is not easy since almost all dopaminergic treatments can induce or trigger orthostatic hypotension: MAO inhibitors, dopamine agonists and, less so, levodopa. Other medications, such as antihypertensives, sildenafil or α-blockers also need to be considered.

Appropriate steps to avoid symptomatic orthostatic hypotension involve hygienic dietary measures, mainly high-salt diet, plenty of isotonic fluid and elastic stockings. When symptoms persist, medications can be tried, including pyridostigmine (25 mg two times per day), fludrocortisone (0.1 mg one to three times a day), domperidone (10 mg three times a day), droxidopa (300 mg three times a day), and midodrine, a selective α-adrenergic agonist that induces vasoconstriction and increases blood pressure, (2.5–10 mg three times a day).

Gastrointestinal complications

Dysphagia is common in Parkinson's disease, typically in its late stages.[1] It results from the loss of coordination

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in the normal steps of deglutition as well as oropharyngeal bradykinesia. Dysphagia may cause malnutrition with weight loss, high levels of anxiety during each meal for both the patient and carer, impaired medication intake and reduced social contact. It is associated with a high rate of mortality, mainly because of aspiration pneumonia.[37] Early suspicion is essential to avoid these complications. Signs of neurogenic dysphagia include frequent coughing, choking or nasal regurgitation during meals, as well as frequent respiratory infections and drooling. When present, video fluoroscopy and fibreoptic endoscopic evaluation of swallowing should be considered.[2] Management of dysphagia involves a personalised swallowing therapy, depending on the severity. Percutaneous gastrostomy may be a possibility, but it has to be implemented with caution.

A recent review showed how to manage dysphagia that interferes with oral intake of medication. Furthermore, alternative methods of oral levodopa are provided with conversion rates to rotigotine patch from other dopamine agonists and levodopa.[38]

Intestinal pseudo-obstruction, also known as paralytic ileus, is a serious condition that sometimes accompanies severe constipation. It seems to be relatively uncommon (2.4%).[39] Abdominal distension, pain, nausea and vomiting characterise intestinal pseudo-obstruction, but in advanced patients with cognitive deterioration it can be difficult to diagnose, presenting with a prominent confusional state and poor response to levodopa.

During the acute phase, urgent endoscopic repositioning will be necessary. More severe cases may be complicated by intestinal perforation requiring surgical treatment.[37] Preventive treatment of constipation with prokinetic drugs may help to prevent recurrences.

Sleep-related complications

Excessive daytime sleepiness and sleep attacks

Excessive daytime sleepiness is inappropriate and undesirable sleepiness during waking hours even after adequate night-time sleep. It occurs in about 30% of patients with Parkinson's disease, frequently in those with cognitive decline, and rarely in untreated patients.[40] It can manifest during a conversation or a meal. Depending on when patients fall asleep, it can be a potential source of caregiver distress.

Sudden-onset-sleep or 'sleep attacks' comprise abrupt episodes of unplanned sleep during activities of daily living (ie, eating, driving). They can have disastrous consequences, particularly when they occur during activities that involve a risk for them and/or others, as with driving. Car accidents, falls and traumas may occur in the context of sleep attacks. Reports in the literature cite a prevalence of 13% for sleep attacks in patients under dopaminergic drugs, typically dopamine agonists and less commonly levodopa.[40] Patients need to be warned about sleep attacks as a common adverse effect of dopaminergic treatment before starting these.

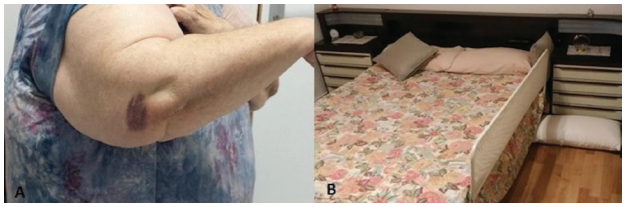

Figure 2 (A) Arm contusion in a patient with Parkinson's disease with REM-sleep behaviour disorder after falling out of bed while enacting a dream during REM-sleep. (B) Protection measures during the night to avoid falls and injuries during the episodes. (Courtesy of Dr. Alex Iranzo [42]). PD, Parkinson's disease; REM, rapid eye movement.

Clinicians should try to identify the main precipitant for excessive daytime sleepiness and sleep attacks. Obstructive sleep apnoea and other causes of poor nocturnal sleep need to be considered. Management is usually to reduce or withdraw those drugs likely to be causing the problem.

REM-sleep behaviour disorder

Rapid Eye Movement (REM)-sleep behaviour disorder is characterised by unpleasant dreams (eg, being attacked or robbed) and vigorous behaviours in which the patients appear to enact their dreams (eg, punching, jumping out of bed, shouting). It occurs in 25%–65% of patients with Parkinson's disease.[41]

Protective measures such as bed rails or chair barricades may help to prevent falling from bed during vigorous dreams. Figure 2 illustrates the consequences of vivid dreams and their subsequent protective measures. Some patients hit their partner during sleep. Clonazepam is the treatment of choice for this sleep disorder despite the lack of randomised, placebo-controlled trials to evaluate its efficacy and safety. The starting dose is 0.25 mg or 0.5 mg at bedtime, increased progressively to a usual dose of 1–2 mg per night. It can aggravate sleep apnoea and so must be used with caution. When clonazepam is ineffective or not well tolerated, melatonin may be considered.[42]

FALLS

Falls are a hallmark of disease progression in Parkinson's disease, occurring in 50%–60% of cases, resulting in reduced mobility and functional regression.[43] They usually result from impaired postural reflexes and can be triggered by events such as freezing of gait, severe dyskinesias and orthostatic hypotension.[36] Because of nocturia, patients may fall at night when walking to the toilet.

Fractures are the most common complications of falls. They take the patient to a reduced mobility state and subsequently increase the risk of death.[43] Subdural haematoma can also be a major consequence of recurrent falls but they are surprisingly uncommon,

Table 3 Complications in the setting of device-aided therapies

	Deep-brain stimulation	Levodopa-carbidopa intestinal gel	Apomorphine
Procedure	Surgery	Percutaneous endoscopy gastrostomy	Subcutaneous infusion
	Intracranial haemorrhage Venous infarction Pneumoencephalus Dyskinesia storm Air embolus	Pneumoperitoneum Peritonitis Gastrointestinal haemorrhage	Not described
Device	Hardware-related	Gastrointestinal pump	Pump
	Infection of external system Skin erosions at the level of the neurostimulator Fracture of extension wire End of life battery Accidental stimulator switch off (eg, environmental factors such as magnetic forces)	Breakdown of connexions Unintentional removal Obstruction of the intraduodenal tube (eg, kinking) Pressure ulcers of intraduodenal tube on intestinal wall Bezoar Pump dysfunction	Subcutaneous nodules Pump dysfunction
Treatment	Stimulation	Levodopa-carbidopa gel	Apomorphine
	Dyskinesia storm Gait unsteadiness Worsening of dysarthria Behavioural changes, hypomania, depression	Unpredictable offs Biphasic dyskinesias Confusion, hallucinations Malabsorption (B_{12}, B_6 vitamin deficiency), polyneuropathy, Guillain-Barré-like syndrome	Nauseas Hypotension Daytime somnolence Confusion, hallucinations Unpredictable offs Dyskinesias Haemolytic anaemia Eosinophilic syndrome

considering the frequency of falls in Parkinson's disease. Many patients with recurrent falls develop a fear of walking, markedly affecting their personal autonomy.

Essential measures to avoid recurrent falls include: home-prevention measures (removing obstacles), physical support (walking stick, walking assistant and wheelchair) and addressing potential triggers such as nocturia, orthostatic hypotension, off periods, dyskinesias.[2] Patients at high risk of falls should receive special attention, including those with freezing of gait, cognitive impairment and poor postural reflexes. There is some evidence to support exercise,[44] but most of the studies showed inconsistent benefit for falls prevention.

EMERGENCIES AND COMPLICATIONS OF DEVICE-AIDED THERAPIES

Device-aided therapies include deep-brain stimulation, levodopa-carbidopa intestinal gel, and apomorphine subcutaneous injections and infusion. These are indicated to treat response fluctuations, such as recurrent disabling offs and dyskinesias refractory to standard therapy.[9] Deep-brain stimulation is also used for drug-refractory tremor. Emergencies and complications related to device-aided therapies are not uncommon, and require prompt medical attention since they are generally associated with significant aggravation of Parkinson's disease symptoms (table 3).

Deep-brain stimulation

This comprises an implantable neurostimulation system that modulates a pathological brain network using a guided, non-ablative and reversible technique. After the surgery patients are invariably instructed to contact the implanting centre or a predetermined movement disorder team with experience in this technique in case of sudden unexplained re-emergence of parkinsonism, severe dyskinesias or appearance of unexpected abnormal behaviours.

Table 3 and figure 3 illustrate common complications related to surgery and the implanted material.

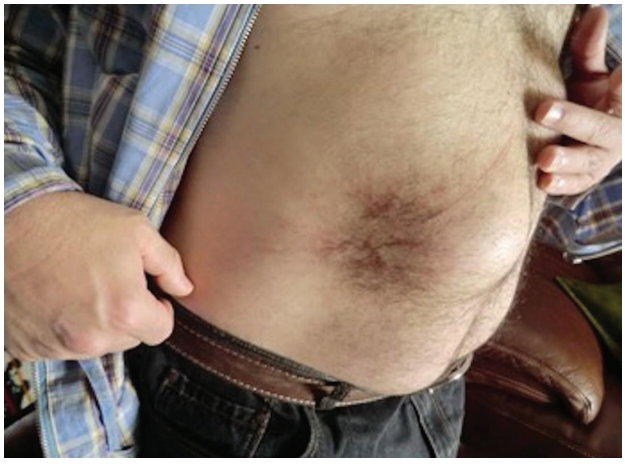

Figure 3 Hardware complication of deep brain stimulation: skin lesion induced by electric current after break of extension cable connecting with the subcutaneous pacemaker.

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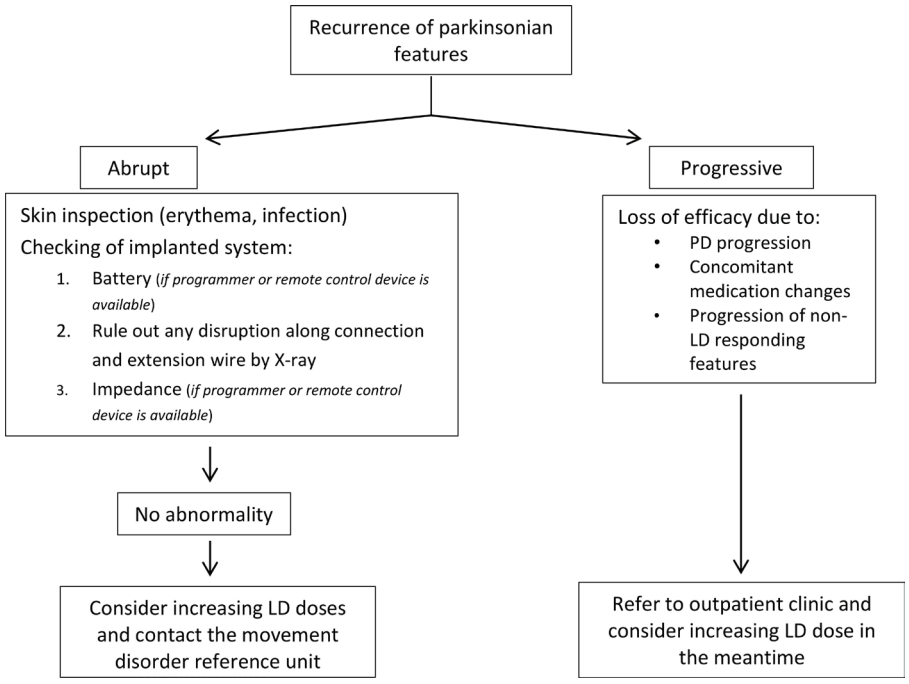

Figure 4 An algorithm approach for DBS efficacy loss. DBS, deep-brain stimulation; LD, levodopa.

Complications can also relate directly to the effects of stimulation on neural structures. Changes made in the stimulation parameters, for example, can lead to severe problems that take the patient to the emergency department. Most frequent of such problems are dyskinesias, sometimes ballistic, worsening of parkinsonism, gait problems, and behavioural changes such as disinhibition, depression and hypomania.[45] Patients with post-surgical depression may have an increase suicide risk, especially during the first year after the surgery.[46] Thus, clinicians need to be cautious with postoperative depression management and refer patients for psychiatric evaluation to achieve a better and close approach from the beginning.

The general neurologist attending an implanted patient with a subacute or sudden worsening of their clinical condition should rule out non-deep brain stimulation causes (as described earlier) and then refer the patient to an expert centre, where appropriate measures such as determining battery life or impedance of the implanted system can be implemented. If there is a suspicion that the cause of the motor aggravation relates to malfunctioning of the implanted material, then clinicians should obtain plain radiographs along the system to locate loss of integrity, such as electrode migration or lead fracture. In addition, oral levodopa may have to be increased while awaiting a more thorough evaluation (figure 4).[47] Among other serious consequences, interruption of stimulation can lead to rhabdomyolysis due the recurrence of severe tremor or aspiration pneumonia because of dysphagia related to worsening of parkinsonism.[45] Prolonged severe parkinsonism should at all costs be avoided or a parkinsonism-hyperpyrexia-like picture may ensue.

Levodopa-carbidopa intestinal gel infusion

The levodopa-carbidopa intestinal gel was designed to solve the pulsatile dopaminergic stimulation after oral levodopa administration. By a continuous delivery of levodopa via percutaneous endoscopic gastrostomy into the jejunum, it can provide steady plasma levodopa concentration. Each package contains 2 g of levodopa and 500 mg carbidopa, generally enough for patients' daily requirements.[9] Adverse events related to this procedure are not uncommon.[48] They can be related to procedure (gastrostomy), infusion system and administered drug (levodopa/carbidopa) (table 3).

Although 95% of patients present an adverse event over the course of the therapy, this proportion decreases over time.[8] Fortunately they are usually reversible events that do not result in permanent treatment interruption. Most frequent are those complications related to the infusion system, such as dislocation of the jejunal tube and catheter migration. An infrequent but potentially dangerous complication related to the infusion system is a bezoar formation, a retained concretion of indigestible material located around the jejunal catheter that can cause an intestinal obstruction.[48] Abdominal pain, flatulence and constipation are the main symptoms. If suspected, patients need a gastroduodenoscopy to verify its location and proceed to its extraction.

Proper education of patients and caregivers is crucial on how to maintain daily care of the stoma and measures to avoid prolonged constipation to prevent long-term complications.

An acute/subacute polyneuropathy resembling Guillain-Barré syndrome has been rarely described among patients under levodopa-carbidopa intestinal gel.[49] After ruling out other treatable causes of acute

Box 3 Key measures for the prevention of complications

1. Parkinson's disease nurse specialists should support patients and caregivers by clarifying concerns and implementing a treatment plan.
2. Patients, caregivers and medical staff are responsible for bringing all the medication updated, and paying attention to medication timings.
3. If at all possible, avoid changing abruptly or changing more than one antiparkinsonian medication at a time.
4. Patients and caregivers should be provided with a list of drugs capable of worsening parkinsonism.
5. Patients taking dopamine agonists should be informed about sleep attacks and risk of impulse-control disorders before starting treatment and regularly during follow-up.
6. Periodically, at least annually, review falls, sleepiness, cognition, autonomic disturbances and psychiatric symptoms.
7. Disease rehabilitative therapy should be proposed to minimise complications such as falls and swallowing problems.
8. In case of elective admission, it is important to plan in advance how to make medication changes. If oral medication intake is limited, consider transdermal agonists, enteral administration of usual medication, and levodopa-carbidopa intestinal gel infusion.

polyneuropathy (ie, endocrine, metabolic, immunological, infective disorders), such cases require stopping treatment infusion, followed by prompt medical treatment based on intramuscular B_{12} and oral folate supplementation. As a preventive measure, it is important to maintain a close control of weight and monitor B_{12} vitamin and folate levels during this therapy.[9] In addition, in those patients with previous polyneuropathy, vitamin supplementation should be taken into account before starting this treatment, therefore neurophysiological studies will be useful to rule out any pre-existing nerve damage before patients start the treatment.[49]

Apomorphine subcutaneous injections and infusion

Apomorphine is an alternative therapy for patients with disabling motor and non-motor fluctuations poorly controlled with conventional treatment. It is a potent dopamine agonist with a short-acting effect that makes it effective in complicated situations such as off dystonia episodes or unpredictable disabling off.[5 9] Subcutaneous injections are used as a rescue therapy when a rapid on is needed. The effect is quick and lasts 45–90 min. Patients needing more than three to six injections per day are best treated with a continuous infusion therapy.[50]

Overall, studies report improvement of off time of 50%–80%. Its effect on dyskinesias is more controversial. Reductions may occur after a few weeks or months of continuous therapy and mostly if large reduction in levodopa dose can be achieved.[51]

Both apomorphine subcutaneous injections and infusion are safe in terms of procedure but can cause adverse events related to the drug itself. These include nausea, hypotension, excessive somnolence and neuropsychiatric problems, such as confusional state, impulse control disorder and dopamine dysregulation syndrome.[50] Subcutaneous nodules develop in 37% of cases treated with infusions; although these are usually not severe and can be managed with non-pharmacological measures, the treatment may need to be stopped.[52]

Prominent motor complications such as severe dyskinesia or offs in the context of apomorphine infusion are rare in comparison to other advanced therapies. Sudden offs can be explained by a pump malfunction, and dyskinesias by a medication overdose or erratic infusion timings.[52]

STRATEGIES TO PREVENT COMPLICATIONS

Prompt diagnosis and intervention are the basis to guarantee a good prognosis for most complications. It is important to note that medication changes cause the large majority of these problems.

Based on the quality standards for Parkinson's disease published by the National Institute for Health and Care Excellence[53] and the American Academy of Neurology,[54] we suggest several measures for preventing or, at least, minimising serious complication in Parkinson's disease (box 3).

The prevention of complications in hospitalised patients is also important. Problems generally relate to dopaminergic medication prescription. It is easy to get

Key points

- Most emergencies in patients with Parkinson's disease are caused by changes in dopaminergic therapy.
- The most common emergencies relate to aggravation of motor symptoms, but serious non-motor complications (such as psychosis, orthostatic hypotension or sleep attacks) may also occur.
- Implanted device-aided therapies (deep-brain stimulation, levodopa-carbidopa intestinal gel, apomorphine subcutaneous infusion) may have potentially serious complications, mostly relating to the device itself.
- Prevention requires that clinicians recognise the most common precipitating factors for serious complications in Parkinson's disease (abrupt therapy changes and underlying systemic disease).
- Prompt attention to the earliest signs by caregivers and health professionals, and early intervention by Parkinson's disease nurse specialists, will minimise serious consequences.

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dose and timing of medications wrong that can cause marked distress and have disastrous consequences, hence it is crucial to check the updated treatment with patients and relatives.[2] The role of the Parkinson's disease nurse is important regarding questions about treatment dosage and updates in the medication regimen.[53] If patients are admitted for medical conditions unrelated to Parkinson's disease, it is important to acquaint other specialists and nursing staff with medications that need to be avoided, such as certain antiemetic and antipsychotic drugs.

With elective surgery, it is important to know how long the postoperative period will last without being able to take oral medication. In case of a major intervention, especially abdominal surgery with inherent difficulties of gastrointestinal absorption it is crucial to consider alternative administration routes of dopaminergic medication, such as dispersible preparations, nasogastric administration, transdermal dopamine agonist and apomorphine. When prompt dopamine replacement is required, higher dose of rotigotine (more than 16 mg/24 hours) and immediate release of pramipexole through nasogastric tube should be considered or at least discussed with the specialist pharmacist and movement disorders unit staff.[38]

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