Emergencies in Parkinson's Disease

**Severe Motor Fluctuations**

Motor fluctuations in Parkinson's disease typically are not severe enough to need urgent interventions; however, some patients may present extremely disturbing and dramatic 'off' periods, especially when they occur suddenly, associated with prominent akinesia, dysautonomia, and psychiatric features, such as anxiety and panic. In these instances, history should look for potential triggers or aggravating factors, including infections, dopaminergic medication changes, and inclusion of antidopaminergic drugs. Management involves combined approaches: fragmentation of daily doses of levodopa, crushed tablets, controlled-release or dispersible levodopa, subcutaneous dopamine agonists, monoamine oxidase B (MAO-B) and catechol-*O*-methyltransferase (COMT) inhibitors, and elective stereotactic surgery.[[2]](javascript:newshowcontent('active','references');)

**Parkinsonism–Hyperpyrexia and Dyskinesia–Hyperpyrexia Syndromes**

Parkinsonism–hyperpyrexia syndrome (PHS) mimics neuroleptic malignant syndrome (NMS) in patients with Parkinson's disease.[[3]](javascript:newshowcontent('active','references');) It is characterized by hyperthermia, dysautonomia, altered consciousness, severe rigidity, and elevated serum creatine kinase levels. PHS may be triggered by infections, hot weather, dehydration, and, particularly, reduction or withdrawal of antiparkinsonian agents (levodopa, dopamine agonists, and amantadine). Commonest situations in which PHS occurs in the context of dopaminergic treatment discontinuation include noncompliance, hospital admission due to comorbidities, or as part of the preoperative procedure for stereotactic surgery. Interestingly, recurrent PHS was described after discontinuation of subthalamic nucleus deep brain stimulation. Potentially fatal complications include venous thrombosis, pulmonary embolism, aspiration pneumonia, and renal failure. Treatment is based on supportive measures and reinstitution of adequate dopaminergic therapy. Occasionally, dantrolene is necessary.[[3]](javascript:newshowcontent('active','references');)

***Dyskinesia–hyperpyrexia syndrome (DHS)*** consists of severe dyskinesias leading to muscle exhaustion, rhabdomyolysis, hyperthermia, and confusion. It shares some of the features of PHS; however, dyskinesias – not rigidity – predominate. In addition, DHS, contrarily to PHS, should be treated by cautiously reducing the dosage of dopaminergic drugs.[[4]](javascript:newshowcontent('active','references');)

**Acute Parkinsonism/Acute Worsening of Parkinsonism**

Acute severe de-novo Parkinsonism is uncommon, most frequently caused by exposure to potent dopamine receptor blockers (DRBs), such as neuroleptics and antiemetics. Other rare causes include hypoxic–ischemic encephalopathy, intoxications, acute hydrocephalus, and infections.[[3,5,6]](javascript:newshowcontent('active','references');) [Table 1](javascript:newshowcontent('active',%20'T1');) lists the broader differential diagnosis.

**Table 1.  Differential diagnosis for acute Parkinsonism**

|  |
| --- |
| Cause |
| Drug induced |
| Neuroleptics |
| Antiemetics |
| Anticonvulsants |
| Cytotoxic agents |
| Antidepressants |
| Intoxications |
| Carbon monoxide |
| Methanol |
| Organophosphates |
| 1-Methyl-1–4-phenyl-4-proprionoxypiperidine (MPTP) |
| Manganese |
| Cyanide |
| Disulfiram |
| Structural |
| Subdural hematoma |
| Hydrocephalus |
| Strategic ischemic lesions |
| Tumors |
| Infections/postinfectious/inflammatory |
| Viral encephalitis |
| HIV |
| Postinfectious |
| Autoimmune |
| Metabolic |
| Pontine and extrapontine myelinolisis |
| Diabetic uremia |
| Hepatic encephalopathy |
| Genetic |
| Rapid-onset dystonia parkinsonism |
| Acute decompensation in Wilson's disease |
| Functional |

Acute worsening of motor symptoms in Parkinson's disease, unrelated to disease progression, typically occurs because of concurrent medical conditions, such as urinary or respiratory tract infections, metabolic disturbances, or neurological disorders (subdural hematoma, spinal cord lesion, brain tumor, etc.).[[1,3,7]](javascript:newshowcontent('active','references');)

For both acute situations, treatment should be focused on resolution of underlying etiologic processes. Occasionally, symptomatic treatment with dopaminergic agents is required.[[8]](javascript:newshowcontent('active','references');)

**Acute Psychosis in Parkinson's Disease**

Psychosis occurs in up to half of cases with Parkinson's disease throughout the disease course, frequently associated and triggered by the same agents used to treat the motor symptoms; however, acute clinical conditions (infectious, metabolic, or neurological disorders) may play a role.[[8,9]](javascript:newshowcontent('active','references');) Manifestations include visual hallucinations, delusions, confusion, and agitation. After treatment of potential comorbidities, a stepwise withdrawal of potentially contributing agents is recommended, starting with anticholinergics, followed by MAO-B inhibitors, dopamine agonists, amantadine, and COMT inhibitors. Introduction of an antipsychotic (clozapine or quetiapine) may be necessary.[[3,5,8]](javascript:newshowcontent('active','references');)

**Neuroleptic Malignant Syndrome**

NMS is an idiosyncratic abrupt reaction to DRB.[[10]](javascript:newshowcontent('active','references');) Often, agents include 'classic' neuroleptics; however, newer 'atypical' agents have all also been implicated, the safest being clozapine and quetiapine.[[11]](javascript:newshowcontent('active','references');) In addition, NMS can occur with other dopamine-blocking drugs or as PHS, after abrupt withdrawal of dopaminergic agents.[[1,3,12,13]](javascript:newshowcontent('active','references');)

Usually, symptoms start during the first 2 weeks of treatment initiation or dosage change.[[14]](javascript:newshowcontent('active','references');) Risk factors include abrupt dose escalation, depot formulations, male sex, young age, use of lithium and selective serotonin reuptake inhibitors (SSRIs), high temperatures, dehydration, exhaustion, extrapyramidal syndromes, and previous NMS episode ( [Table 2](javascript:newshowcontent('active',%20'T2');) ).[[15]](javascript:newshowcontent('active','references');) All age groups can be affected, most cases are in their fourth and fifth decades.[[10,12,15]](javascript:newshowcontent('active','references');) Mortality remains high between 20 and 30% of cases.[[1,3]](javascript:newshowcontent('active','references');) Most survivors recover without sequelae; however, some present cognitive and motor abnormalities, including rigidity, tremor, and dystonia.[[16]](javascript:newshowcontent('active','references');)

Diagnostic criteria combine the tetrad of hyperthermia, rigidity, altered mental status, and dysautonomia. Associated signs include tremor, dystonia, chorea, myoclonus, seizures, ataxia, hyporeflexia, and extensor plantars.[[3,10,12]](javascript:newshowcontent('active','references');) In addition, laboratory changes include raised serum creatine kinase (>1000 IU/l), impaired liver, renal, and coagulation status tests, leukocytosis, electrolyte disturbances, proteinuria, rhabdomyolysis, and myoglobinuria.[[1,10,12]](javascript:newshowcontent('active','references');) The most important differential diagnoses are serotonergic syndrome, malignant hyperthermia, and catatonia.[[1,12,13]](javascript:newshowcontent('active','references');)

Treatment depends on recognition, exclusion of differential diagnoses, medication withdrawal, supportive care, and pharmacological interventions depending on severity and presence of complications.[[1,3,10]](javascript:newshowcontent('active','references');) Severe symptoms require intensive care management and pharmacological reduction of rigidity (benzodiazepines or dantrolene) and dopaminergic blockage (bromocriptine or levodopa), as well as control of agitation.[[10,12,13]](javascript:newshowcontent('active','references');) Electroconvulsive therapy has been used anecdotally.[[17]](javascript:newshowcontent('active','references');) Neuroleptics should be stopped for at least 2 weeks after the acute phase. Management of the underlying psychiatric condition can be then restarted with low doses, slow titration, avoiding lithium, and with close observation to prevent recurrence.[[1,10]](javascript:newshowcontent('active','references');)

**Serotonergic Syndrome**

Serotonergic syndrome results most often from the combination of two or more agents that enhance serotonergic activity or concentration in the central nervous system.[[1,3,12,18]](javascript:newshowcontent('active','references');) This underrecognized syndrome presents with agitation, mental status changes, myoclonus, ataxia, postural instability, hyperreflexia, rigidity, and dysautonomia after changes in serotonergic drug regimen.[[1,19]](javascript:newshowcontent('active','references');) Onset is typically abrupt but some patients report insidious or recurrent subtle cognitive decline, behavioral abnormalities, and tremor with postural changes days to weeks before the full-blown syndrome develops.[[18]](javascript:newshowcontent('active','references');)

Serotonergic syndrome is a predictable reaction. The offending drugs are those that cause excessive brainstem and spinal cord serotonin or 5-hydroxytryptamine (5-HT) type 1A receptor stimulation.[[18,20]](javascript:newshowcontent('active','references');) The most common implicated agents are listed in [Table 2](javascript:newshowcontent('active',%20'T2');), but although any of them can potentially cause serotonergic syndrome, a combination is usually needed, with greater risk for monoamine oxidase inhibitors or SSRIs concomitantly used with any other serotonergic agent.[[18]](javascript:newshowcontent('active','references');) Although doses taken are commonly within therapeutic limits, 20% of cases occur secondary to overdose.[[1,21]](javascript:newshowcontent('active','references');) Other risky circumstances include rapid titration, addition or switch to a new agent without proper washout period, liver or renal disease, endogenously reduced monoamine oxidase A activity, cytochrome P4502D6 enzyme inhibition, and old age.[[19]](javascript:newshowcontent('active','references');)

[MAOIs act by inhibiting the activity of [monoamine oxidase](https://en.wikipedia.org/wiki/Monoamine_oxidase), thus preventing the breakdown of [monoamine neurotransmitters](https://en.wikipedia.org/wiki/Monoamine_neurotransmitter) and thereby increasing their availability. There are two [isoforms](https://en.wikipedia.org/wiki/Isoform) of monoamine oxidase, MAO-A and MAO-B. MAO-A preferentially [deaminates](https://en.wikipedia.org/wiki/Deamination) [serotonin](https://en.wikipedia.org/wiki/Serotonin), [melatonin](https://en.wikipedia.org/wiki/Melatonin), [epinephrine](https://en.wikipedia.org/wiki/Epinephrine), and [norepinephrine](https://en.wikipedia.org/wiki/Norepinephrine). MAO-B preferentially deaminates [phenethylamine](https://en.wikipedia.org/wiki/Phenethylamine) and certain other [trace amines](https://en.wikipedia.org/wiki/Trace_amine); in contrast, MAO-A preferentially deaminates other trace amines, like [tyramine](https://en.wikipedia.org/wiki/Tyramine), whereas [dopamine](https://en.wikipedia.org/wiki/Dopamine) is equally deaminated by both types.]

Serum or cerebrospinal fluid serotonin levels are useless for diagnosis, which is established on clinical grounds.[[12,18]](javascript:newshowcontent('active','references');) The starting point is obviously the history of medication exposure, added by clinical manifestations. The most widely used diagnostic criteria require the positive medication history along with any of the following: myoclonus, agitation or diaphoresis; unexplained hyperthermia; hypertonia; and tremor and hyperreflexia, after other causes have been ruled out.[[22]](javascript:newshowcontent('active','references');) Seizures, renal failure, and coagulopathy may occur.[[1,3,18,20]](javascript:newshowcontent('active','references');) Laboratory abnormalities include metabolic acidosis, rhabdomyolysis, elevated white cell count, and serum aminotransferase and creatinine levels. Differential diagnoses include cocaine or lithium overdose, anticholinergic poisoning, malignant hyperthermia, and NMS, each readily distinguished from serotonergic syndrome based on medication exposure history.[[12,19,22]](javascript:newshowcontent('active','references');)

Treatment requires medication withdrawal, enough to improve half of all cases.[[1,3]](javascript:newshowcontent('active','references');) Persistent/severe symptoms require pharmacologic treatment. Nonspecific 5-HT receptor blockers (cyproheptadine and methysergide) have been credited with shortening the syndrome's duration.[[1,23]](javascript:newshowcontent('active','references');) Other agents include benzodiazepines, chlorpromazine, and propranolol. Treatment of seizures, arrhythmias, coagulopathy, rigidity, and hyperthermia may be necessary.[[23]](javascript:newshowcontent('active','references');) Serotonergic syndrome is potentially fatal, mortality rates range from 2.4 to 12%.[[20,21]](javascript:newshowcontent('active','references');) As in NMS, reintroduction of treatment of the underlying psychiatric disorder requires close monitoring, low dose, and slow titration.[[19,21]](javascript:newshowcontent('active','references');)

**Malignant Hyperthermia**

Malignant hyperthermia is a rare genetic muscle disorder that occurs when a mutation-positive patient is exposed to inhalation anesthetics or depolarizing muscle relaxants.[[24]](javascript:newshowcontent('active','references');) Malignant hyperthermia manifests with abrupt hyperthermia, fluctuations in blood pressure, hypercarbia, hyperkalemia, metabolic acidosis, rigidity, and rhabdomyolysis.[[25]](javascript:newshowcontent('active','references');)

Malignant hyperthermia results from uncontrolled calcium flux across muscle membrane, in more than half of cases due to a dominant mutation on the gene encoding skeletal muscle type-1 ryanodine receptor.[[26]](javascript:newshowcontent('active','references');) Dantrolene can be effective treatment, along with correction of metabolic and electrolyte abnormalities. At present, with appropriate management and awareness, mortality is less than 5%.[[24,25]](javascript:newshowcontent('active','references');) Comparison of NMS, serotonergic syndrome, and malignant hyperthermia is shown in [Table 2](javascript:newshowcontent('active',%20'T2');).

**Chorea and Ballismus**

Acute severe chorea can result from numerous causes including drug exposures, toxic/metabolic derangements, vascular disease, infectious/postinfectious, and autoimmune disorders, leading to hyperthermia and rhabdomyolysis if not recognized and treated aggressively.

Sydenham chorea is a childhood-onset manifestation of rheumatic fever.[[27]](javascript:newshowcontent('active','references');) Additional features include behavioral changes, weakness, hypotonia, and vocalizations. The diagnosis is clinical with supportive laboratory tests often showing elevated [alpha]-streptolysin-O and [alpha]-DNAase-B titers.[[28]](javascript:newshowcontent('active','references');) The most widely used symptomatic treatment of chorea under these circumstances is valproic acid at doses of 10–25 mg/kg/day. DRB should be reserved for severe and refractory cases because of the associated risk of complications.[[27,28]](javascript:newshowcontent('active','references');) Chorea gravidarum has been historically associated with a past history of rheumatic fever or Sydenham chorea, but chorea arising during pregnancy can also be drug induced or associated with systemic lupus erythematosus, antiphospholipid antibody syndrome, syphilis, and encephalitis.[[29]](javascript:newshowcontent('active','references');) In the case of classic chorea gravidarum, chorea typically begins in the first trimester. One-third of cases resolve spontaneously before delivery, and the remainder within hours after delivery. When necessary, after the first trimester, low-dose haloperidol has been shown to be effective.[[27,29]](javascript:newshowcontent('active','references');)

Ballism defines larger amplitude, coarse, forceful movements often occurring acute and unilaterally. Ballism and chorea may in fact represent a continuum of hyperkinetic movements differentiated by speed and amplitude.[[30]](javascript:newshowcontent('active','references');) The most common cause of hemiballism is vascular, classically taught to indicate a lesion to the contralateral subthalamic nucleus. However, this topography is uncommon and lesions in multiple areas have been implicated.[[31,32]](javascript:newshowcontent('active','references');) Nonketotic hyperglycemia can result in unilateral or bilateral ballism, typically in elderly females, as a presenting feature of diabetes mellitus or in established cases.[[32,33]](javascript:newshowcontent('active','references');) Brain MRI T1-weighted images typically show high signal in the contralateral putamen and occasionally in the globus pallidus, findings thought to result from petechial hemorrhages.[[33]](javascript:newshowcontent('active','references');) Abnormal movements tend to subside when the metabolic disturbance normalizes, but may be permanent. Other causes of acute ballism and chorea are listed in [Table 3](javascript:newshowcontent('active',%20'T3');). Most cases resolve spontaneously within months. [Table 4](javascript:newshowcontent('active',%20'T4');) shows treatment options when required. Treatment-refractory patients may need stereotactic surgery.[[5]](javascript:newshowcontent('active','references');)

**Dystonia**

Patients with inherited, acquired, or idiopathic dystonia can develop acute worsening with severe, continuous contractures, a phenomenon referred to as 'dystonic storm' or status dystonicus. Several factors can precipitate status dystonicus including infection, medication changes, and trauma.[[34,35]](javascript:newshowcontent('active','references');) As the sustained contractures can be life threatening, ICU admission is necessary, in addition to a stepwise pharmacological approach that includes anticholinergics, DRB, dopamine depletors, sedation, and paralyzing agents. In refractory status dystonicus, stereotactic surgery has been tried.[[35]](javascript:newshowcontent('active','references');)

Acute dystonic reactions can be seen after exposure to DRB, typically within 24 h of exposure. Risk is increased in men and when the dose is rapidly titrated.[[1,30]](javascript:newshowcontent('active','references');) Manifestations can combine blepharospasm, cervical, laryngeal or limbs dystonia, and oculogyric crisis. Life-threatening respiratory compromise can occur when the larynx or pharynx are affected. Management includes parenteral anticholinergics or antihistamines, after the precipitating agent is discontinued.[[1]](javascript:newshowcontent('active','references');)

**Myoclonus**

Myoclonus can present emergently, especially in the inpatient setting, and be a harbinger of an underlying toxic metabolic derangement, drugs reaction (as in serotonergic syndrome and NMS), or cerebral hypoxia. Two myoclonic syndromes can result from cerebral anoxia: myoclonus status epilepticus (MSE) and Lance Adams syndrome (LAS).[[36,37]](javascript:newshowcontent('active','references');) MSE usually indicates poor prognosis and begins within hours of the anoxic event with spontaneous, unrelenting, generalized, or multifocal myoclonus in comatose patients.[[36]](javascript:newshowcontent('active','references');) LAS or postanoxic myoclonus has a delayed onset, with stimulus sensitive and action-induced movements.[[37]](javascript:newshowcontent('active','references');) LAS may improve spontaneously over years or be unrelenting. When myoclonus is particularly disabling, treatment may include clonazepam, valproic acid, and levetiracetam ([Table 4](javascript:newshowcontent('active',%20'T4');)).[[30]](javascript:newshowcontent('active','references');)

Finally, myoclonus may be a drug reaction induced by the same agents that cause serotonergic syndrome and NMS, added by opiates, gabapentin, antibiotics, and spinal anesthetics.

**Tics**

Although the majority of patients with tic disorders have a benign course, neurologic injury due to intense exacerbation may be an uncommon emergency, including cases in which head thrusting with violent neck movements resulted in compressive neuropathies, myelopathies, and subdural hematoma.[[38]](javascript:newshowcontent('active','references');) Factors known to markedly worsen tics include fatigue, stress, infection, and medications (stimulants, tricyclic antidepressants, and SSRIs). After the precipitating factor has been removed, pharmacologic treatment may be necessary using neuroleptics and dopamine depleting agents.[[30]](javascript:newshowcontent('active','references');)

**Conclusion**

The scope of the movement disorders provided in this review was intended to focus on life-threatening syndromes that diverge from the archetypal potentially severe but chronic, insidious disorders seen on most specialized ambulatory care clinics. Some of them have uncertain diagnostic criteria and are managed using an assemblage of anecdotal treatment options. These disorders may, therefore, present as sources diagnostic confusion and treatment dilemmas in emergency settings. Future directions should be directed not only to advance the basic and clinical aspects of these disorders but also to disseminate means for more accurate and prompt diagnosis and interventions.

**Table 2.  Comparison of features and management of neuroleptic malignant syndrome, serotonergic syndrome, and malignant hyperthermia**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Neuroleptic malignant syndrome** | **Serotonergic syndrome** | **Malignant hyperthermia** |
| Age/sex predisposition | Young men | None | Children, young adults |
| Triggering factor | Idiosyncratic | Drug combination/overdose | Gene mutation |
| Onset | Acute | Subacute | Acute |
| Causative agents | Classic/newer antipsychotics, antiemetics, L-dopa withdrawal | SSRIs, SNRIs, tricyclic antidepressants, MAOIs, L-tryptophan, amphetamines, cocaine | Volatile anesthetics, succinylcholine |
| Fever | +++ | ++ | +++ |
| Confusion | +++ | +++ | + |
| Dysautonomia | +++ | +++ | +++ |
| Motor features | Tremor, rigidity | Myoclonus, rigidity, stereotypies, hyperreflexia | Rigidity |
| Diaphoresis | +++ | ++ | +++ |
| Elevated serum creatine kinase | +++ | ++ | +++ |
| Elevated serum transaminases | +++ | + | − |
| Metabolic acidosis | + | + | ++ |
| Pharmacologic treatmenta | Bromocriptine, amantadine, dantrolene | Cyproheptadine, methylsergide | Dantrolene |

MAOIs, monoamine oxidase inhibitors; NMS, neuroleptic malignant syndrome; SNRIs, serotonin–norepinephrine inhibitors; SSRIs, selective serotonin reuptake inhibitors.

aPrior to any form of pharmacological treatment, patients should be stabilized and withdrawn of causative agent.

**Table 3.  Differential diagnosis of acute chorea and ballismus**

|  |  |
| --- | --- |
| Vascular | Ischemic/hemorrhagic stroke |
|  | Malformations |
|  | Cerebral anoxia |
|  | Postpump chorea |
|  | Polycythemia vera |
| Metabolic | Nonketotic hyperglycemia |
|  | Hypoglycemia |
|  | Uremic encephalopathy |
|  | Hyperthyroidism |
|  | Hypoparathyroidism |
| Structural | Basal ganglia lesion or mass |
|  | Cerebellar lesion or mass |
|  | Thalamotomy or subthalomotomy |
| Infectious | Cryptococcal granuloma |
|  | Toxoplasmosis |
|  | Tuberculoma |
|  | HIV encephalitis |
| Autoimmune | Postinfectious/Sydenham chorea/chorea gravidarum |
|  | Systemic lupus erythematosus |
|  | Antiphospholipid antibody syndrome |
|  | Scleroderma |
|  | Behcet disease |
|  | Polyarteritis nodosa |
|  | Sarcoidosis |
|  | Multiple sclerosis |
|  | Paraneoplastic (CV2/CRMP-5 antibodies) |
| Iatrogenic | Anticonvulsants |
|  | Oral contraceptives |
|  | Levodopa |
|  | Cocaine |
|  | Amphetamines |
|  | Morphine |
|  | Methadone |
|  | Alcohol |

**Table 4.  Pharmacological treatment of movement disorders**

|  |  |  |  |
| --- | --- | --- | --- |
| **Movement disorder** | **Medication class** | **Medication** | **Initial – maximum daily dose (mg)** |
| Chorea | Neuroleptic | Haloperidol | 0.5–8 |
|  |  | Risperidone | 0.5–6 |
|  | Dopamine-depleting agent | Tetrabenazine | 12.5–75 |
|  | Benzodiazepine | Clonazepam | 0.5–6 |
|  | Anticonvulsant | Valproic acid | 750–1500 |
| Ballism | Dopamine-depleting agent | Tetrabenazine | 12.5–200 |
|  | Neuroleptic | Haloperidol | 0.5–8 |
| Myoclonus | Anticonvulsant | Levetiracetam | 500–3000 |
|  |  | Valproic acid 750–1500 |  |
|  | Benzodiazepine | Clonazepam | 0.5–6 |
| Tics | Neuroleptic | Pimozide | 1–10 |
|  |  | Haloperidol | 0.5–8 |
|  | Dopamine-depleting agent | Risperidone | 0.5–6 |
|  | Antihypertensives | Tetrabenazine | 12.5–75 |
|  |  | Clonidine | 0.1–0.6 |
|  |  | Guanfacine | 1–3 |
| Dystonic storm | Anticholinergic | Trihexyphenidyl | 5–20 |
|  |  | Diphenhydramine | 25–400 |
|  | Dopamine blocker | Haloperidol | 0.5–8 |
|  |  | Pimozide | 1–10 |
|  | Dopamine-depleting agent | Tetrabenazine | 12.5–75 |
| Acute dystonic reaction | Anticholinergic | Benzotropine | 1–6 |
|  |  | Diphenhydramine | 25–400 |