Problem-Based Review

Problem based review: A patient with Parkinson's disease

A Arora & P Fletcher

Abstract

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by bradykinesia, tremor and/or rigidity, often with gait disturbance and postural instability.

In addition to these typical features, patients with PD may experience further problems related to the disease itself or to the medications used to treat it. These comorbid problems include neuropsychiatric conditions (including psychosis, hallucinations, excessive daytime sleepiness, anxiety, depression, fatigue and dementia) as well as problems associated with autonomic nervous system function such as bowel and bladder function. PD can also present in emergency situations with a 'neuroleptic malignant like picture' and acute psychosis. It is not uncommon to see motor fluctuations due to drug interactions and 'withdrawal' symptoms following dose reduction of dopamine agonists.

In patients with PD, disturbances of mental state constitute some of the most difficult treatment challenges of advanced disease, often limiting effective treatment of motor symptoms and leading to increased disability and poor quality of life. While some of these symptoms may be alleviated by antiparkinsonian medication, especially if they are 'off-period' related, treatment-related phenomena are usually exacerbated by increasing the number or dosage of antiparkinsonian drugs. Elimination of exacerbating factors and simplification of drug regimens are the first and most important steps in improvement of such symptoms.

Keywords and Abbreviations

Parkinsonism Hyperpyrexia Syndrome (PHS), Neuroleptic Malignant Syndrome (NMS), Neuroleptic Malignant like Syndrome (NMLS), Serotonin Syndrome (SS), Levodopa induced Dyskinesia (LID), Deep brain stimulation (DBS), Dopamine receptor Agonists (DA), Dopamine agonist withdrawal syndrome (DAWS), Dopamine replacement therapy (DRT).

Key Points

1. *In any elevation of body temperature during the course of anti-parkinsonian drug treatment PHS should be considered as a cause until excluded.*[10]
2. *In a patient who is 'nil by mouth' it must be ensured that a nasogastric tube is placed to administer regular PD medications to prevent withdrawal syndromes including PHS/NMLS. If that is not possible, a transdermal patch of Rotigotine (a dopamine-receptor agonist), is currently approved as monotherapy. Apomorphine as subcutaneous injections 'on demand' or continuous subcutaneous injection by means of a pump is also an option if expertise is available.*[23]
3. *The MAO-B inhibitors like Selegeline should be used only at recommended doses (10mg OD) in PD and with caution when combined with other antidepressants, including tricyclics and SSRIs, because of the risk of causing the serotonin syndrome. Among SSRI drugs, sertraline appears to be the safest in this respect.*[24]
4. *If antiparkisonian drugs are thought to be contributing to psychiatric symptoms or 'levodopa misuse', a gradual reduction or stopping of dopaminergic dugs is needed (Table 3)*
5. *The clinician needs to differentiate between Dopamine agonist withdrawal features and 'end-of-dose' wearing off of levodopa.*[25]
6. *Cases of 'dopamine replacement therapy' addiction, in which patients develop a maladaptive pattern of medication use and drug withdrawal symptoms reminiscent of a substance abuse disorder have been well documented in PD. This phenomenon is referred to as the 'dopamine dysregulation syndrome'.*

Alok Arora
MRCP (London)
Frenchay Hospital

Peter Fletcher
FRCP (London)
Cheltenham General Hospital
Cheltenham

Correspondence:
Alok Arora
Frenchay Hospital
North Bristol Hospitals NHS Trust
Bristol
BS16 1LE
Email: alokjarora@hotmail.com

Case Scenario

A 67 year old man with an 8-year history of PD was admitted following a fall at home. On initial assessment he was found to have postural hypotension and nitrite-positive urine dip. The patient noted that his involuntary movements (dyskinesias) were worse than usual.

His postural hypotension was attributed to PD itself and also his multiple anti-parkinsonian medications (4mg ropinirole once a day, 100/25 mg co-careldopa 5 times a day and 10 mg selegiline once a day). He was also taking 20 mg sertraline OD.

What are the common reasons for hospital admission in patients with PD?

As PD progresses, falls become increasingly common, with up to 70% of patients with advanced PD reporting at least 1 fall per year.[1] Postural instability or freezing of gait are responsible for up to 80% of all falls in patients with PD.[2] There is a 3-month fall rate of 46%, with the best predictor of falling being a history of 2 or more falls in the previous year.[3] Injuries occur in approximately 25% of falls, with hip fractures a common result. Postural instability is not levdopa responsive, making treatment a challenge. The Global Parkinson's Disease Survey Steering Committee[4] examined why patients with PD present to emergency departments, the most common reasons were *not* Parkinson's disease specific; infectious disease 21%-32%; cardiovascular/cerebrovascular 12%-26%; gastrointestinal 8%-11%; and metabolic 2%-6%.

Of problems directly related to PD, the most common were falls and trauma (13%-27%), motor fluctuations/dyskinesia (8%), and psychiatric disturbances (8%). Motor fluctuations are common in

advanced PD and are seen in 40% of patients by 4 to 6 years with an increasing frequency of 10% per year.[5]

While generally not dangerous, motor fluctuations are one of the more common disease specific reasons that patients seek emergency treatment. During 'off periods', prominent rigidity, bradykinesia, and postural instability may develop, making it impossible for patients to care for themselves or to walk. Psychiatric features may become pronounced, including depressed mood, anxiety, and panic.

Dysautonomia, including tachycardia, diaphoresis, and variations in blood pressure, may occur leading to evaluation in the Emergency Department. In these situations, investigations should search for a potential secondary cause if the changes are acute. A careful medication history may be necessary to ensure that no recent changes have been made to the antiparkinsonian regime. Patients should also be questioned about the addition of medications to their regimen, particularly dopamine receptor blockers (see Table 1). In a patient with PD who presents with multiple falls and acute worsening of their neurological symptoms, subdural hematoma should be considered.[6]

What is the role of levodopa in PD dyskinesias?

Levodopa induced Dyskinesia (LID) is usually not dangerous and is most often managed in the outpatient setting. However, severe dyskinesia may lead to weight loss, rhabdomyolysis and dehydration.[6]

Generalized dyskinesias may be complicated by involvement of respiratory muscles, with patients reporting symptoms of dyspnoea, tachypnoea, chest wall discomfort, and involuntary grunting.[7]

Failure to recognize respiratory dyskinesia may lead to unnecessary testing. Greater emphasis on medical and medication history may improve the diagnosis of respiratory dyskinesia in the emergency setting. Treatment of dyskinesias should ideally include lowering (or at least temporarily holding) the levodopa dosage. Benzodiazepines may be useful to treat concomitant anxiety. Neuroleptics should not be used. Long-term management for chronic dyskinesia may involve the addition of amantadine or deep brain stimulation (DBS).[8]

Case Scenario continued:

During the course of the admission, the patient's ropinirole was tapered off completelely over three days. Four days post admission the patient was found in a 'confused, rigid and hallucinating' state with a temperature of 40.2C despite having received paracetamol regularly. On examination he had increased tremor and stiffness of all four limbs, profuse sweating, tachypnoea, tachycardia and an inability to fully open his mouth. The patient was alert with a Glasgow Coma Scale (GCS) of 14/15, but was disorientated and experiencing visual hallucinations.

What is the most likely reason for this acute deterioration?

The Parkinsonism Hyperpyrexia Syndrome (PHS) is a rare (0.3% of PD patients/year) but potentially fatal complication seen in Parkinson's disease (PD) patients. It is characterised by mental status changes, muscle rigidity, hyperthermia and autonomic dysfunction. Mortality of up to 4% has been reported but an additional one-third of patients have permanent sequelae. PHS should always be considered in a patient with Parkinsonism who presents with an acute deterioration. Parkinsonism hyperpyrexia syndrome may be indistinguishable from Neuroleptic Malignant Syndrome (NMS) except that it occurs in patients with pre-existing Parkinsonism and is often referred to as Neuroleptic Malignant-Like Syndrome (NMLS).

Levenson *et al.* in 1985[9] suggested a definition for NMS using the sum of 3 major or 2 major *plus* 4 minor criteria in an appropriate clinical setting (Table 2); these criteria can also be helpful in diagnosing NMLS/PHS.[10]

Although withdrawal of levodopa is still the most common cause of PHS, withdrawal of other dopaminergic agents, including amantadine, dopamine agonists, and catechol-O-methyltransferase inhibitors have be implicated.[11]

Case Scenario continued:

The patient was cooled via external ice packs and cooled IV fluids. A nasogastric (NG) tube was inserted and an additional dose of his usual co-careldopa was given and ropinirole was restarted. The Creatine Kinase (CK) was 845 U/L (50-200 U/L) and repeat urine dipstick testing showed microscopic haematuria. The patient's condition improved over the several hours and his muscle tone and temperature returned to baseline over the next few days.

The major differential diagnosis of PHS (and NMS) is 'serotonin syndrome' (see Table 3). Tricyclic antidepressants (TCAs) such as nortriptyline and amitriptyline have been used widely for the empirical treatment of depression in PD.[12] They may be poorly tolerated owing to their anticholinergic properties

Table 1. Drugs causing interactions with anti-PD drugs.

Antiemetics such as metoclopromide and prochlorperazine
Neuroleptics (typical and atypical)
Antiepileptics
Antidepressants
Chemotherapeutic agents
Amiodarone

Table 2. Diagnostic Criteria for NMS. [9]

Criteria	Features
Major	*Fever, rigidity, and elevated creatinine kinase level*
Minor	*Tachycardia, abnormal blood pressure, tachypnoea, altered consciousness, diaphoresis (profuse sweating) and leukocytosis*

and amitriptyline may also cause unacceptable sedation in PD patients at higher doses. However, the anticholinergic properties of TCAs may also improve parkinsonian symptoms and sedation may be a desired effect when given at bedtime to improve sleep. The combination of MAO-A inhibitors and TCAs or SSRIs is considered to pose an 'unacceptable risk' of serotonin syndrome, whereas this risk is considered to be low for the combination of selegiline with other antidepressants.

MAO-A inhibitors like Moclobemide should not be co-prescribed with levodopa (because of the potential risk of hypertension), or with SSRIs or TCAs (because of the risk of causing a potentially serious serotonin syndrome). This syndrome has rarely been described with the MAO-B inhibitor selegiline on its own.[12]

Serotonin Syndrome *(SS)*[13,14] may have additional clinical features such as myoclonus, hyperreflexia, seizures, and mood alteration (restlessness, elevated mood). This overlap may relate to the impact elevated serotonin levels have on lowering dopamine levels. Treatment consists of discontinuation of the causative agent, supportive therapy, and cyproheptadine hydrochloride for severe cases. Serotonin syndrome may resolve quickly or is potentially fatal. Like PHS, the rarity and seriousness of SS precludes large randomized trials.

Table 3. Comparison of Neuroleptic Malignant and similar Syndromes (PHS/NLMS) and Serotonin Syndrome.[13]

	Neuroleptic Malignant Syndrome	Serotonin Syndrome
Onset	*Sub-acute (days), commonly occurs when starting or increasing dose of antipsychotics but may occur at any time during drug treatment*	*Acute (hours), usually precipitated by starting/ increasing dose of a serotonergic agent or by the addition of another drug with serotonergic activity*
Resolution	*Gradual (average 9 days)*	*Rapid, usually improves in < 24 h*
Physical examination	• *Altered sensorium (90%)* • *Muscle rigidity (90%)* • *Autonomic Dysfunction (90%)* • *Hyperthermia (90%)*	• *Altered sensorium (50%)* • *Muscle rigidity (50%)* • *Autonomic Dysfunction (50%-90%)*
Laboratory abnormalities	• *Elevated creatine kinase level (90%)* • *Elevated hepatic transaminase levels (75%)* • *Leukocytosis (90%)*	• *Elevated creatine kinase level (20%)* • *Elevated hepatic transaminase levels (10%)* • *Leukocytosis (15%)*
Background	• *Parkinson's disease if PHS suspected*	• *Offending drugs (Table 3)*

Case Scenario continued:

Overnight, the patient developed increased agitation, experienced visual and auditory hallucinations and was deemed at ' high risk' of further falls, the on call doctor was asked to provide sedation.

How should acute agitation be managed in a patient with PD?

Psychosis in PD is a common reason for inpatient admission and a strong predictor of nursing home placement.[15] It is more commonly encountered in PD patients with dementia, occurring in 45% to 64% of such patients. Visual hallucinations are more common than auditory hallucinations and usually consist of complex, formed visual images.[16] In PD, psychosis (and/or delirium) may be precipitated by metabolic derangements, infections and changes in drug therapy including the addition of any dopaminergics or anticholinergics. It is important to identify and manage restless legs syndrome (RLS)and REM sleep behaviour disorder in such a situation.

A thorough workup for metabolic or infectious disorders is indicated. The daily levodopa dose may also need to be lowered. Antipsychotic medication treatment can be started and is often necessary to resolve the psychosis. Useful antipsychotics include clozapine and quetiapine.

Clozapine has the most robust evidence base. Despite the lack of compelling evidence for quetiapine[17] it is often prescribed because of clozapine's risk of agranulocytosis and the need for monitoring of full blood counts on a frequent basis.

If the antiparkisonian drugs are thought to be contributing to psychiatric symptoms, a gradual reduction or stopping of the dopaminergic dugs is needed and Table 4 suggests a useful way to do this.

There is an increased risk of stroke in elderly patients with dementia treated with risperidone or olanzapine, and it has been advised that risperidone and olanzapine should not be routinely used for the treatment of behavioural symptoms or psychosis in dementia.[18]

While the differentiation between psychiatric symptoms related to 'off-period' and those independent of motor fluctuations can sometimes be difficult, it has important treatment implications. Antidepressant, anxiolytic or analgesic medications are usually ineffective for such 'off-period' related phenomena, but they typically resolve when off-periods are terminated by antiparkinsonian

Table 4. Reduction and withdrawal of antiparkinsonian medication in psychosis in Parkinson's disease.[18]

Selegiline
Anticholinergics
Amantadine
Dopamine agonists
COMT-inhibitors
Controlled-release levodopa
Standard levodopa

Table 5. Recommended doses for atypical antipsychotics in Parkinson's disease

Drug starting dose	Maintenance dose
Quetiapine 12.5 mg/d	*12.5–150 mg/d*
Clozapine 6.25 mg/d	*10–50 mg/d*

medication.Thus, increasing rather than decreasing the dose of levodopa, or the addition of a COMT-inhibitor or a dopamine agonist, is the recommended treatment approach to these 'off-period' psychiatric phenomena. In particular, subcutaneous apomorphine rescue injections have been shown to provide rapid improvement of such psychiatric symptoms in addition to the alleviation of motor symptoms.[19]

Case Scenario continued

The patient's anti PD medications were increased and he was discharged only to be readmitted 6 weeks later with 'erratic' behaviour. His wife said that he has never been so active and of note she had particularly noted purposeless and repetitive patterns of behaviour.

What is dopamine dysregulation syndrome?

The syndrome of dopamine dysregulation (or levodopa misuse) is difficult to recognize in parkinsonian patients who experience 'off-period' dysphoria. However, the need for unusually large doses of levodopa, liberal and uncontrolled modifications of drug-regimens and increasing demands/requests for higher doses despite severe dyskinesia may point towards the diagnosis. Drug hoarding or seeking behaviour and aggressive or violent behaviours may also occur which can lead to significant impairment of occupational and social functioning. A number of other psychiatric presentations may be associated with this syndrome, including punding (repetitive, purposeless behaviours, such as dismantling electrical equipment) which may also be seen in amphetamine or cocaine addiction. This syndrome is difficult to manage but is best treated with gradual reduction of dopaminergic drug doses and symptomatic treatment of psychiatric complications.[20]

Hypersexuality can be a dose-dependent side effect of dopaminergic treatment, which is mostly reported by carers rather than patients and can put serious strain on the relationship between a carer and patient. On careful questioning there are often other symptoms suggestive of hypomania present although hypersexuality may occur in isolation.[20]

Case Scenario continued:

Following the diagnosis of 'dopamine dysregulation' the patient's dopamine agonist was reduced but he slowly developed 'withdrawal' features.

What is the dopamine agonist withdrawal syndrome?

Dopamine agonist (DA) withdrawal syndrome (DAWS) is defined as a severe, stereotyped cluster of physical and psychological symptoms that correlate with DA withdrawal in a dose-dependent manner, cause clinically significant distress or social/occupational dysfunction, are refractory to levodopa and other Parkinson disease medications, and cannot be accounted for by other clinical factors.[21]

More recently, dopamine agonists (DAs) have been shown to produce behavioural addictions, with an estimated 14% to 17% combined prevalence of impulse control disorders (ICDs) such as pathological gambling, compulsive eating, compulsive buying, risk-seeking driving behaviour and hyper sexuality in DA-treated patients.[21]

The clinical manifestations of DAWS are highly stereotyped and closely resembled other psycho stimulant withdrawal syndromes, with prominent psychiatric (anxiety, panic attacks, dysphoria, depression, agitation, irritability, fatigue) and autonomic (orthostatic hypotension, diaphoresis) manifestations. In all cases, the symptoms temporally correlate with DA withdrawal and rapidly and selectively remit with DA replacement, consistent with a drug-specific withdrawal syndrome. [21]

New-onset 'dopamine dysregulation syndrome' was a common consequence of DAWS and often clouded the clinical picture. Levodopa, other PD medications, antidepressants, anxiolytics, and psychotherapy are of no benefit in mitigating DAWS symptoms. One of the major barriers to the recognition and diagnosis of DAWS was that the symptoms closely resembled those of typical end-of-dose wearing-off, leading to the false expectation that they would be alleviated by compensatory levodopa. This misinterpretation was compounded by the fact that some subjects used motor terminology (e.g. "stiff," "unable to move") when referring to these non motor symptoms. The similarity between DAWS, 'dopamine dysregulation syndrome', and 'end-of-dose' wearing-off of levodopa is not surprising given that all three can be regarded as dopamine replacement therapy (DRT) withdrawal syndromes.

Would the onset of cognitive impairment affect the patient's anti-PD treatment?

A smaller proportion of patients with PD develop clinical dementia. In prospective community- or clinic-based studies approximately 30% of non-demented patients develop clinical dementia over a follow-up of 4 years.[22] Risk factors for dementia in PD include older age, more severe disease, presence of hallucinations and lower mini mental scores at baseline, but not disease duration or age at onset, suggesting that dementia in PD is likely to reflect an interaction of the neuropathology of the basal ganglia and of age-related pathology.[25]

The clinical characteristics of Dementia with lewy bodies (DLB), overlaps with PD and include parkinsonism with frequent falls, dementia, hallucinations and delusions with marked fluctuations, susceptibility to deterioration of parkinsonism with antipsychotics, REM sleep behaviour disorder, depression and syncope.

The differentiation of DLB and dementia in PD is based on the temporal pattern, and DLB can be diagnosed if the dementia is present at the onset of parkinsonian symptoms or begins within the first year of motor symptom.[20] When dementia develops in patients with PD, antiparkinsonian drug treatment usually requires adjustment, as such patients are often more susceptible to side effects, e. g. of drugs with anticholinergic properties. [22]

Conflict of interest

This study was funded entirely by the authors and they have no conflict of interest with any third party.

References

1. Wood BH, Bilclough JA, Bowron A, *et al.* Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. *J Neurol Neurosurg Psychiatry* 2002; **72(6):** 721–725.
2. Michalowska M, Fiszer U, Krygowska-Wajs A, *et al.* Falls in Parkinson's disease: causes and impact on patients' quality of life. *Funct Neurol* 2005; **20(4):**163–168.
3. Pickering RM, Grimbergen YAM, Rigney U, *et al.* Ameta-analysis of six prospective studiesof falling in Parkinson's disease. *Mov Disord* 2007; **22(13):**1892–1900.
4. Global Parkinson's Disease Survey Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. *Mov Disord* 2002; **17:** 60–67
5. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 2001; **16(3):** 448–458.
6. Factor SA, Molho ES. Emergency department presentations of patients with Parkinson's disease. *Am J Emerg Med* 2000; **18(2):** 209–215.
7. Weiner WJ, Goetz CG, Nausieda PA, *et al.* Respiratory dyskinesias: extrapyramidal dysfunction and dyspnea. *Ann Intern Med* 1978; **88:** 327–31.
8. Pahwa R, Factor SA, Lyons KE, *et al.* Practice parameter: treatment of Parkinson disease motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; **66:** 983–95.
9. Levenson JL. Neuroleptic malignant syndrome. *Am J Psychiatry* 1985 Oct; **142(10):**1137–45.
10 Takubo H, Harada T, Hashimoto T, *et al.* A collaborative study on the malignant syndrome in Parkinson's disease and related disorders. *Parkinsonism Relat Disord* 2003; S31-41.
11. Factor SA. Fatal Parkinsonism-hyperpyrexia syndrome in a Parkinson's disease patient while actively treated with deep brain stimulation. *Mov Disord* 2007; **22(1):** 148–149.
12. Movement Disorders Task Force (2002) Treatment of depression in idiopathic Parkinson's disease. *Mov Disord* 17: 112–119.
13. Mills KC. Serotonin syndrome: a clinical update. *Crit Care Clin* 1997; **13(4):** 763–783.
14. Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome. Presentation of 2 cases and review of the literature. *Medicine* 2000; **79:** 201–9.
15. Aarsland D, Larsen JP, Tandberg E, *et al.* Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc* 2000; **48(8):** 938–942.
16. Mosimann UP, Rowan EN, Partington CE, *et al.* Characteristics of visual hallucinations in Parkinson disease dementia and dementia with Lewy bodies. *Am J Geriatr Psychiatry* 2006; **14(2):**153–160.
17. Miyasaki JM, Shannon K, Voon V, *et al.* Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; **66(7):** 996–1002.
18. Anette Schrag. Psychiatric aspects of Parkinson's disease, An Update. *J Neurol* 2004; **251:** 795–804.
19. Maricle RA, Nutt JG, Valentine RJ, *et al.* Dose-response relationship of levodopa with mood and anxiety in fluctuating Parkinson's disease: a double-blind, placebo-controlled study. *Neurology* 1995; **45:**1757–1760.
20. Giovannoni G, O'Sullivan JD, Turner K, Lees AJ (2000) Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. *J Neurol Neurosurg Psychiatry* 68: 423–428.
21. Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in Parkinson's disease. *Arch Neurol* 2010; **67(1):** 58–63.
22. Giladi N, Treves TA, Paleacu D, *et al.* Risk factors for dementia, depression and psychosis in long-standing Parkinson's disease. *J Neural Transm* 2000; **107:** 59–71.
23. Frankel JP, Lees AJ, Kempster PA, *et al.* Subcutaneous apomorphine in the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry 1990;* **53:** *96–101.*
24. Leo RJ. Movement disorders associated with the serotonin selective reuptake inhibitors. *J Clin Psychiatry* 1996; **57(10):** 449.
25. Hughes AJ, Daniel SE, Kilford L, *et al.* Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. *JNNP* 1992; **55:** 181–184.