

## REVIEW ARTICLE

## Parkinson's disease and anaesthesia

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Parkinson's disease is an increasingly common disease of elderly patients who present a particular anaesthetic challenge. This review explores the epidemiology, aetiology, pathogenesis, and pathophysiology of the condition, particularly the possible role of genetic factors. The clinical features are described in detail and recent advances in medical management are highlighted. Controversies surrounding the use of the newer drugs and possible advances in neurosurgical interventions are discussed. Particular anaesthetic problems in patients with Parkinson's disease are respiratory, cardiovascular, and neurological. Potential drug interactions are described and recommendations are made about suitable anaesthetic techniques.

*Br J Anaesth* 2002; **89**: 904–16

**Keywords:** anaesthesia; complications, Parkinson's disease

Involuntary tremulous motion, with lessened muscular power, in parts not in actions and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses being uninjured.

James Parkinson, 1817.<sup>92</sup>

Parkinson's disease has been known since biblical times, but it was only in the nineteenth century that the syndrome was formally described by James Parkinson and termed 'the shaking palsy'.<sup>92</sup> In 1879, Charcot noted additional features including autonomic dysfunction.<sup>15</sup> The association between the substantia nigra and Parkinson's disease was discovered in 1893, but it was only in the latter half of the twentieth century that the neuropathological and neurochemical characteristics of the disease were elucidated and logical treatment strategies devised.<sup>6 10 19 105</sup>

Although the aetiology of Parkinson's disease is unknown, age has been identified as the most consistent risk factor; Parkinson's disease affects approximately 3% of the population over 66 yr of age.<sup>76</sup> Parkinson's disease is an important cause of perioperative morbidity and, with an increasingly elderly population, it will be encountered with greater frequency in surgical patients. Drugs used in anaesthesia may interact with anti-parkinsonian medication

and there is controversy about the optimal anaesthetic management of patients with Parkinson's disease.

### Epidemiology

Parkinson's disease occurs world wide, affecting all ethnic groups, with a very slight male preponderance.<sup>139</sup> The prevalence increases exponentially between 65 and 90 yr; approximately 0.3% of the general population and 3% of people over 65 yr have it.<sup>76</sup> The EUROPARKINSON study found an overall prevalence of 2.3% for parkinsonism and 1.6% for Parkinson's disease in a survey of 14 636 participants aged over 65 yr in five European countries.<sup>109</sup> As many as 24% of the subjects with Parkinson's disease were newly diagnosed at the time of the study. This highlights the difficulty of diagnosis and emphasizes that many elderly hospital patients may have undiagnosed Parkinson's disease. However, a recent study of more than 120 000 patients in London general practices suggested the incidence was considerably less.<sup>114</sup> Five to ten per cent of patients have symptoms before the age of 40 yr (so-called young-onset Parkinson's disease). The lowest reported incidence is among Asians and African blacks and the highest is amongst whites. The disease was first formally described during the Industrial Revolution,

suggesting that exogenous toxins may have a causative role, but descriptions of conditions resembling Parkinson's disease are found in literature dating back thousands of years BC.

## Aetiology

The syndrome of *parkinsonism* (clinical conditions which resemble idiopathic Parkinson's disease) may have a number of different causes such as arteriosclerosis, diffuse central nervous system degenerative disease, repeated head trauma, tumour, metabolic defects such as Wilson's disease, heavy metal, or carbon monoxide poisoning. Drug-induced parkinsonism results from dopamine receptor block by drugs such as phenothiazines, butyrophenones, and metoclopramide. The observation of parkinsonian symptoms in heroin addicts who accidentally used 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), a pethidine analogue, has led to the development of a useful animal model for the syndrome.<sup>59</sup> An epidemic of encephalitis lethargica in the 1920s was responsible for an outbreak of early onset parkinsonism with associated severe rigidity and respiratory complications.

Although the aetiology of Parkinson's disease is unknown, it has long been hypothesized that neurodegeneration is induced by genetic, environmental, or infectious disorders. Age is the single most consistent risk factor and it has been estimated that there is a cumulative lifetime risk of one in 40 for developing Parkinson's disease.<sup>100</sup> Loss of pigmented cells in the substantia nigra is the most consistent finding in Parkinson's disease and normally the quantity of nigral cells diminishes from 425 000 to 200 000 at 80 yr. In Parkinson's disease, the substantia nigra shows marked depletion of cells (<100 000) with replacement gliosis. In addition, tyrosine  $\beta$ -hydroxylase, the rate-limiting step in dopamine synthesis, also diminishes. The remaining cells contain the highly characteristic eosinophilic Lewy bodies. However, the pattern of nigral cell loss in Parkinson's disease differs from that due to normal ageing. In Parkinson's disease, cell loss is predominantly from the ventrolateral tier of the substantia nigra, but this region is relatively spared in normal subjects.<sup>23</sup> Furthermore, if ageing is the primary mechanism that accounts for the time course of functional decline, it does not adequately explain the huge inter-individual variability in rates of clinical progression of the disease.<sup>41 138</sup>

After ageing, a family history is the strongest predictor of an increased risk of developing the disease, although the role of a common environment must also be considered.<sup>116</sup> Relatively high rates of concordance have been identified amongst monozygotic twins, when one twin had young-onset disease.<sup>123</sup> Most of the available evidence supports an autosomal dominant inheritance of the disease, but many patients do not show this pattern of inheritance. This may reflect the fact that the causative genes have low penetrance or that the disease is multifactorial. To date, the identifica-

tion of genes involved in the dopaminergic system has proved disappointing. The discovery of two distinct mutations in the  $\alpha$ -synuclein gene (SNCA) located on chromosome 4q appeared to be a major breakthrough.<sup>55 98</sup> Alpha-synuclein is a highly conserved, abundant 140 amino acid protein of unknown function that is expressed mainly in presynaptic nerve terminals in the brain.<sup>33</sup> It appears to be a major component of Lewy bodies, the hallmark intracytoplasmic eosinophilic inclusion bodies, and its occurrence in Parkinson's disease suggests that this disease also belongs to those conditions, such as Alzheimer's, attributable to toxic protein aggregation.<sup>14</sup> Mutations in  $\alpha$ -synuclein were reported in a number of unrelated families with a strong family history of Parkinson's disease, but several studies have failed to locate this genetic defect in other families or in sporadic cases, suggesting that Parkinson's disease is only rarely caused by such defects.<sup>55</sup> Similarly, attempts to implicate the detoxifying enzymes, debrisoquine 4-hydroxylase (CYP2D6) or *N*-acetyltransferase 2, in the pathogenesis of Parkinson's disease have been inconclusive.<sup>5 107</sup>

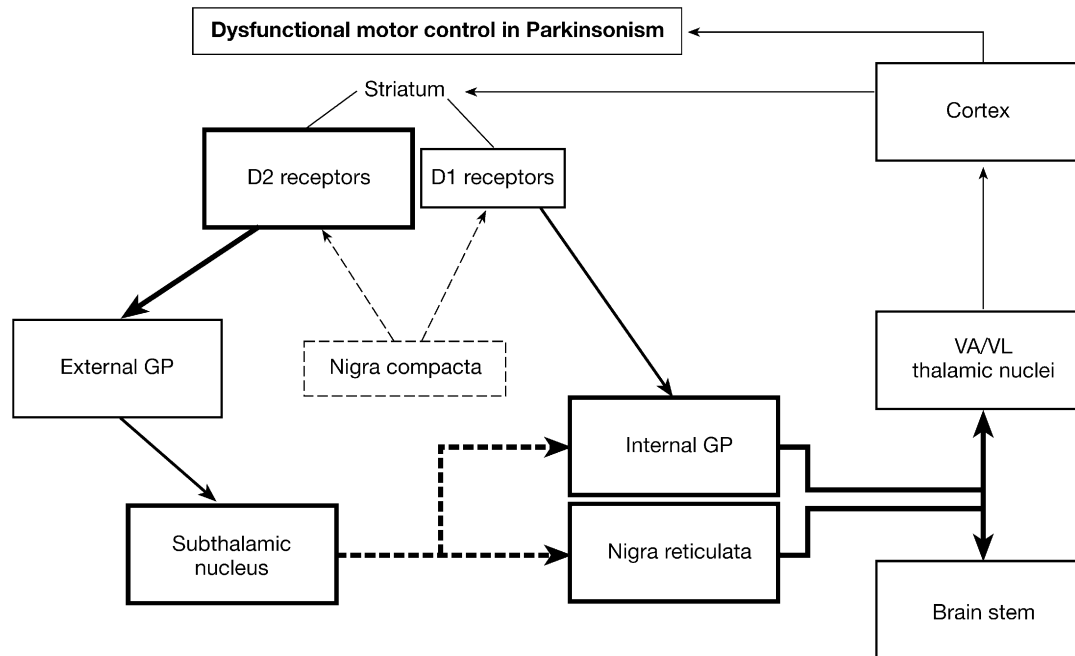
Parkinson's disease was first described during the industrial revolution suggesting that environmental toxins may play a role in its pathogenesis. The discovery of MPTP-induced parkinsonism lends further weight to this theory.<sup>59</sup> A rural environment has been associated with an increased risk of developing Parkinson's disease, suggesting that agents such as herbicides or pesticides may have an aetiological role, although this is limited to approximately 10% of patients with Parkinson's disease.<sup>115</sup> Cigarette smoking has been shown consistently to reduce the risk of developing Parkinson's disease,<sup>39 79</sup> although this may be restricted to those with a relatively young age at onset of the disease.<sup>127</sup> This effect has been attributed to inhibition of monoamine oxidase type B by products of tobacco combustion. Evidence linking dietary factors to Parkinson's disease is inconclusive, although one study has shown a lower vitamin E intake in patients with Parkinson's disease compared with controls.<sup>108</sup>

Overall, most cases of Parkinson's disease are likely to result from a combination of genetic and environmental factors and these differ between individuals. Genetic mutations may predispose patients to develop Parkinson's disease if combined with other gene mutations or environmental factors.<sup>71</sup>

## Pathogenesis

Parkinson's disease is characterized by the progressive death of selected, but heterogeneous, populations of neurones, including those dopaminergic neurones of the pars compacta of the substantia nigra. The precise mechanisms responsible for cell death are largely unknown and may be due to mitochondrial dysfunction, oxidative stress, the actions of excitotoxins with excess nitric oxide formation, deficient neurotrophic support, or immune mechanisms.<sup>57</sup>





**Fig 2** Dysfunctional control in Parkinsonism (reproduced with permission).<sup>58</sup>

(D1) receptors on the dendritic spines, and those upon indirect pathway neurones are inhibitory via D2 receptors. Cholinergic internuncial neurones are excitatory to projection neurones and are inhibited by dopamine. In Parkinson's disease, acetylcholine is present in normal amounts in the striatum. However, dopamine deficiency produces imbalance in the dopamine:acetylcholine ratio, thereby aggravating the symptoms of Parkinson's disease. A healthy substantia nigra is tonically active, favouring activity in the direct pathway. Facilitation of the direct pathway is necessary for the supplementary motor cortex to become active before and during movements.

Parkinson's disease is characterized by a loss of dopaminergic neurones in the substantia nigra of the basal ganglia (Fig. 2).<sup>58</sup> A decrease in dopamine production results in facilitation of the indirect pathway because of a lack of D1 facilitation of the direct pathway and of D2 inhibition of the indirect pathway. This dopamine deficient state is associated with increased activity of inhibitory nuclei in the basal ganglia (using the neurotransmitter  $\gamma$ -aminobutyric acid (GABA)), eventually leading to excessive inhibition, and effectively to a shutdown, of the thalamic and brainstem nuclei that receive the outflow from the basal ganglia. Excessive thalamic inhibition results in suppression of the cortical motor system with akinesia, rigidity and tremor, while inhibition of brainstem locomotor areas may contribute to abnormalities of posture and gait.

## Diagnosis and clinical features

Parkinson's disease comprises a classical triad of resting tremor, muscle rigidity, and bradykinesia, with, in addition,

loss of postural reflexes.<sup>57</sup> The clinical signs can remain surprisingly unilateral until the disease is well advanced.<sup>61</sup> Diagnostic difficulty arises because the clinical features may be subtle early in the disease and alternative diagnoses such as arthritis or depression may be considered until the disease progresses. One of the most prominent figures of the twentieth century, Adolf Hitler, suffered from idiopathic Parkinson's disease, which was largely unnoticed despite innumerable public appearances.<sup>30</sup> Furthermore, the classical clinical features are not exclusive to Parkinson's disease but may be exhibited in other, 'parkinsonian', syndromes. The primary process that yields the parkinsonian phenotype is depigmentation of the pars compacta in the substantia nigra and loss of dopaminergic neurones, which terminate in the basal ganglia. Therefore, conditions that affect the brainstem, or disrupt the dopaminergic pathway, or affect the basal ganglia, can present with parkinsonian features. Such conditions include cerebrovascular disease, neoplasia, repeated head trauma and metabolic defects such as Wilson's disease, heavy metal or carbon monoxide poisoning, and other neurodegenerative conditions.<sup>57</sup> Neurodegenerative parkinsonian syndromes may be associated with more extensive pathology in the brain and brainstem, and often have additional clinical features that may be collectively termed 'Parkinson-plus' syndromes. These conditions include progressive supranuclear palsy (PSP) with progressive restriction of vertical eye movements,<sup>63 120</sup> corticobasal degeneration with progressive limb stiffness, clumsiness, weakness, apraxia, and alien limb phenomenon,<sup>110 122</sup> multiple system atrophy<sup>135</sup> embracing olivopontocerebellar atrophy,<sup>32</sup> striatonigral degeneration<sup>134</sup> and Shy-Drager syndrome,<sup>117</sup> and diffuse

Lewy body disease characterized by early dementia and hallucinations.<sup>65</sup> There is no specific test to confirm Parkinson's disease, the diagnosis is made mainly on clinical grounds. Magnetic resonance imaging of the brain is usually normal in Parkinson's disease but may be useful in demonstrating cerebrovascular disease or widespread brainstem atrophy in other neurodegenerative disorders.<sup>113</sup> Autonomic dysfunction is common in parkinsonian disorders and is often present earlier and more severely in the 'Parkinson-plus' syndromes. Sphincter electromyography, reflecting degeneration of Onuf's nucleus, has been shown to be a useful test to distinguish Parkinson's disease from multiple system atrophy or PSP.<sup>130</sup>

In autopsy studies, the final diagnosis of Parkinson's disease was incorrect in over 20% of cases.<sup>42 102</sup> However, a more recent study reported that 8% of untreated patients who had been diagnosed early with Parkinson's disease had a different diagnosis after 7 yr follow-up.<sup>45</sup> The features that are particularly characteristic of idiopathic Parkinson's disease are asymmetry of symptoms (especially tremor) and a good response to L-DOPA;<sup>57</sup> over 90% of patients have a good response to L-DOPA early in the disease. L-DOPA is usually so effective in ameliorating the symptoms of Parkinson's disease that a poor response demands consideration of alternative diagnoses. L-DOPA is the most effective treatment for Parkinson's disease and patients may have very little disability for the first few years of the disease; falls are also relatively infrequent during this phase. However, as Parkinson's disease progresses, other features appear and patients may complain of fluctuations in motor ability, cognitive impairment and depression.<sup>46 119</sup> The later clinical features may reflect progression of the underlying neurodegenerative process beyond the nigrostriatal pathway to affect other brainstem, thalamic, or basal ganglia nuclei or complications of drug treatment, or both.<sup>44</sup> Motor fluctuations in their simplest form are usually related to drug timing. Patients may notice that the effect of L-DOPA wears off about an hour before the next expected dose. The patient may change from a motor state characterized by fairly normal ability to move (termed the 'on' state) to one dominated by bradykinesia or akinesia, termed the 'off' state. The 'off' state does not reflect a return to untreated parkinsonism but probably a rebound worsening of the motor condition.<sup>101</sup> In addition, abnormal movements (termed 'dyskinesias') may occur in either state. 'Off' period dyskinesias tend to be fixed and dystonic, whereas 'on' dyskinesias are thought to be related to peak levels of L-DOPA and are very mobile and choreiform. Occasionally, dyskinesias appear transiently after a dose of L-DOPA has been taken. Therefore, it is important to obtain a detailed history of dyskinesias related to the drug regimen to identify when during the L-DOPA cycle these events occur and whether they are related to wearing off, early or peak dose effects.

The tremor of Parkinson's disease is seen at rest, oscillates at about 4–6 Hz, has a characteristic 'pill rolling'

quality, and ceases at the onset of movement.<sup>24</sup> The tremor becomes less marked with movement (unlike cerebellar tremors), but may be postural (brought out for example by holding a cup and saucer) like essential tremor.<sup>73</sup> However, essential tremor may be differentiated as it is autosomal dominant, often improved by alcohol and not associated with other parkinsonian features.<sup>43 64</sup> Parkinsonian tremor can be brought out by relaxing the patient's arm and asking them to count back from 100, subtracting seven each time. Testing finger-nose (or heel-shin) co-ordination emphasizes that the tremor is present mainly at rest. Rigidity often accompanies the tremor, giving it a 'cogwheeling' feel.<sup>24 81</sup> The best movements to test are flexion-extension at the elbow and wrist. Bradykinesia is a paucity of movement. The movements appear slow and there is a reduction in the amplitude of the finger excursions.<sup>1</sup> In addition to slowness of finger movements, handwriting is affected with micrographia an easily elicitable feature.<sup>74</sup> Facial expression may be affected giving rise to a characteristic, expressionless face. Parkinsonian patients may also demonstrate a variety of primitive reflexes including the glabellar tap sign.<sup>131</sup>

Clinical examination must include an assessment of posture and gait. The patient may have a slightly flexed posture. If the patient is asked to stand with their eyes shut and the examiner perturbs their equilibrium by a gentle push, either backwards or forwards (ensuring that the patient does not fall and hurt themselves), the patient may take several steps either backwards (retropulsion) or forwards (propulsion) before regaining their balance. This is because the postural reflexes are abnormal in Parkinson's disease.<sup>11 125</sup> About 80% of patients with Parkinson's disease experience gait hypokinesia at some stage of the disease.<sup>80</sup> In addition, gait initiation failure and freezing are common. If initiation of gait is impaired, the patient may lean forward to start moving. The gait comprises small steps, which may become more and more rapid (festination) and there may be reduced arm swing. Lack of arm swing on the same side as the tremor is very characteristic. Later in the disease, freezing of gait may become a major problem.<sup>31 73</sup> Patients often have difficulty turning and will turn taking many small shuffling steps on the spot.<sup>80</sup>

Examination of eye movements is very helpful in differentiating idiopathic Parkinson's disease from other parkinsonian conditions. Parkinson's disease patients may show slowness of initiation of voluntary saccades and jerkiness of pursuit movements.<sup>12 47</sup> However, markedly increased latency of voluntary saccades, or restriction and slowing of vertical eye movements with limitation of voluntary up and down gaze, suggests an alternative cause for parkinsonism such as corticobasal degeneration or PSP.<sup>128</sup>

Dysautonomia is often a feature of Parkinson's disease and other parkinsonian syndromes.<sup>16</sup> Patients with Parkinson's disease may suffer from orthostatic hypotension, urinary dysfunction and sleep disorders. Therefore, clinical assessment should include an assessment of these



problems with measurement of arterial pressure lying, and standing, as there may be marked postural fluctuations.

## Treatment of Parkinson's disease

### *Drug therapy*

The aim of treatment of Parkinson's disease is to enable the patient to pursue a normal active lifestyle. The mainstay of treatment is drug therapy using L-DOPA or dopamine receptor agonists. The crucial factor is to educate the patient about the disease and how the drugs are likely to affect them. With guidance, patients can usually adapt a regimen to suit their particular lifestyle. The result may be that they take drugs at apparently peculiar times. A common scenario is that a patient's finely tuned drug regimen is thrown into disarray on admission to hospital when the drug timings are forced into the available boxes on the drug card. It is very important to record the exact times when a patient's drugs are due, and to try to reproduce these as far as practicable in hospital.

### *L-DOPA and dopamine agonists*

The main deficit in Parkinson's disease is lack of availability of dopamine in the basal ganglia, so the logical treatment is to replace this with exogenous dopamine or stimulate the same receptors as endogenous dopamine. It is widely considered that the best treatment for Parkinson's disease is L-DOPA, a prodrug, which is converted to dopamine in the brain.<sup>44 96</sup> L-DOPA is administered in combination with a peripheral DOPA decarboxylase inhibitor to minimize peripheral dopamine side-effects. The alternative approach is to use dopamine agonists. Although these drugs may be very helpful in early Parkinson's disease, the effect is not sustained and patients often require combination therapy with L-DOPA as the disease progresses.<sup>96</sup> Dopamine agonists include bromocriptine,<sup>52</sup> ropinirole,<sup>52</sup> pergolide,<sup>7</sup> pramipexole,<sup>8 77</sup> and cabergoline.<sup>111</sup> Each agonist is effective in improving motor function in Parkinson's disease.<sup>126</sup> The main controversy in deciding whether to start treatment with L-DOPA or a dopamine agonist stems from the observation that initial use of L-DOPA may produce early dyskinesias. As L-DOPA has a short half-life (30–60 min), dopamine receptors are subject to phasic stimulation rather than the tonic stimulation that is thought to occur in normal basal ganglia function.<sup>126</sup> The mechanism of generation of dyskinesia is poorly understood but it is possible that the onset of dyskinesias is related to the short half-life of L-DOPA in the striatum.<sup>44 126</sup> A recent clinical trial confirmed that using a dopamine agonist before starting L-DOPA delayed the onset of dyskinesias,<sup>104</sup> yet L-DOPA remains the most effective agent for relieving symptoms and signs of Parkinson's disease.<sup>118</sup> The debate continues about whether to start treatment with a dopamine agonist or L-DOPA,<sup>78 133</sup> in

younger patients, a dopamine agonist is tried first and then L-DOPA is added, if necessary.<sup>118</sup>

Apomorphine is a short-acting dopamine agonist that is administered subcutaneously, or sometimes sublingually or intranasally.<sup>82</sup> An important side-effect is nausea and vomiting, but with the concurrent use of domperidone it may be well tolerated.<sup>82</sup> It is particularly useful administered as an infusion to smooth out motor fluctuations or rescue patients from 'off' periods.<sup>97</sup> It is not widely available, as expertise supervising the use of infusion pumps is essential.

### *Monoamine oxidase inhibitors*

The type B monoamine oxidase inhibitor, selegiline is also used to treat Parkinson's disease and it prolongs the action of dopamine in the striatum. Selegiline improves the symptoms of Parkinson's disease but in addition there was a suggestion in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study,<sup>93 136</sup> that it may retard progression of the disease independent of its symptomatic effect and exert a neuroprotective effect.<sup>50</sup> The subsequent enthusiasm for selegiline was tempered in the UK by the publication of a report suggesting that, in combination with L-DOPA, it was associated with a 60% increased mortality compared with L-DOPA treatment alone.<sup>62</sup> However, the open labelled trial design, the large number of patients who withdrew from their original treatment assignment, the high mortality in both treatment groups, and the fact that no previous trial had demonstrated selegiline toxicity, made interpretation of the UK trial difficult.<sup>90</sup> There was no increase in mortality associated with selegiline in the DATATOP study.<sup>94</sup> A meta-analysis of trials of selegiline did not confirm an excess of deaths in selegiline-treated patients<sup>91</sup> and a recent case-controlled study reported that Parkinson's disease patients had a higher mortality compared with age-matched controls, but that mortality was not significantly increased by taking selegiline.<sup>20</sup> The role of selegiline in treating Parkinson's disease remains controversial.<sup>82</sup>

### *Alternative therapies*

Within 5 yr of starting therapy for Parkinson's disease, half to two-thirds of patients will experience fluctuations in their motor symptoms.<sup>70</sup> With continued therapy, these fluctuations become more dependent on the plasma concentration of levodopa.<sup>38</sup> To ameliorate the fluctuations, the circulating dopamine concentration must be stabilized. This may be achieved by changing the dosing regimen or using a controlled release preparation of L-DOPA. Alternatively, a combination of L-DOPA and a dopamine agonist may be used. The agonist provides tonic dopamine receptor stimulation during the wearing off period. Another approach is to use catechol-*O*-methyl transferase (COMT) inhibitors, which inhibit the breakdown of dopamine in the periphery

and increase its bioavailability.<sup>38</sup> Thus, COMT inhibitors may smooth out fluctuations in dopamine concentration which contribute to the wearing off, or on-off fluctuations, and improve the amount of 'on' time. The COMT inhibitors in common clinical use are tolcapone and entacapone. However, there is concern over tolcapone producing hepatotoxicity,<sup>89</sup> so entacapone is the preferred drug. If dyskinesias are very marked, amantadine may significantly diminish L-DOPA-induced dyskinesias.<sup>66</sup> Anticholinergic drugs such as benhexol have limited efficacy and many side-effects, which limit their tolerability.<sup>118</sup> They may be useful in early disease to treat tremor (where bradykinesia is not a major problem).

### *Surgical treatment*

An exciting development has been the advent of surgical treatment for Parkinson's disease. Surgical procedures comprise deep brain stimulation, ablative lesions and cell transplantation. Deep brain stimulation has the advantage that it is reversible and adjustable. In Parkinson's disease, the depletion of dopamine in the striatum leads to a series of changes in basal ganglia circuitry.<sup>87</sup> There is hyperactivity in the subthalamic nucleus, which is relayed as increased excitatory drive to the internal segment of the globus pallidus and thence as excessive inhibitory output to the thalamocortical motor projections (Fig. 2). This results in decreased cortical motor output manifested as bradykinesia. Chronic, deep-brain high-frequency stimulation mimics the effect of an ablative lesion. Pallidal stimulation has been reported to have a similar beneficial effect to pallidotomy. Subthalamic nucleus stimulation is the most promising surgical intervention for Parkinson's disease. Several studies have reported marked improvements in rigidity, tremor and bradykinesia. Bilateral stimulation is possible with further improvement in parkinsonian features. Unilateral thalamotomy, or thalamic stimulation, provide effective treatment for contralateral tremor in 75–85% of patients. The procedure is relatively safe if performed unilaterally. Bilateral lesions may produce dysarthria and dysphagia as well as cognitive problems. Pallidotomy involves lesions to the globus pallidus internum, and is effective in reducing contralateral dyskinesia and contralateral 'off' symptoms. Lastly, transplantation of fetal mesencephalic tissue into the striatum of Parkinson's disease patients has been reported to improve symptoms. Fetal grafts have been found to survive for several years and form synaptic connections. However, the technique is still experimental.<sup>56 137</sup>

Dopamine antagonist drugs, which may produce a parkinsonian syndrome or exacerbate the disease, must be avoided perioperatively. Metoclopramide is a surprisingly common cause of this problem. Treating postoperative confusion, or drug-induced psychosis, in Parkinson's disease may be difficult. The introduction of 'atypical' antipsychotic drugs (which have much reduced parkin-

sonian side-effects) has enabled the psychosis to be treated without exacerbating Parkinson's disease. Clozapine has been shown to be particularly effective in this respect<sup>27 95</sup> but causes fatal agranulocytosis in 1–2% of patients. Olazapine, risperidone and quetiapine are other antipsychotics which have been shown to be effective treatment for psychosis with fewer parkinsonian side-effects.<sup>18 29</sup> Another method of managing a Parkinson's disease patient with postoperative confusion is to use a benzodiazepine for sedation. Care must be taken to ensure that there is no respiratory depression, but this approach allows immediate control of the confusion while the cause (anaemia, infection, metabolic disturbance, etc.) is sought and treated.

### **Anaesthetic considerations**

Patients with Parkinson's disease most commonly present for urology, ophthalmological, or orthopaedic procedures, and elderly surgical patients may have undiagnosed Parkinson's disease.<sup>83</sup> Anaesthetic management is also required for pallidotomy, thalamotomy, or neuroaugmentative procedures. Apart from a routine history, physical examination, and preoperative testing, patients with Parkinson's disease require additional assessment. Table 1 summarizes the recommendations for the patient with Parkinson's disease.

### *Respiratory system*

Respiratory abnormalities have been noted in patients with Parkinson's disease since its initial description in 1817 and respiratory complications, particularly aspiration pneumonia, are the most common causes of death in these patients.<sup>41</sup> An obstructive ventilatory pattern has been observed in up to one-third of patients with Parkinson's disease,<sup>85 86</sup> but may also be due to co-existing chronic obstructive pulmonary disease.<sup>86</sup> However, there is evidence that abnormal control and function of the upper airway may be responsible for the airflow limitation observed in extrapyramidal disorders.<sup>129</sup> The intrinsic laryngeal muscles, and probably most of the other muscles surrounding the upper airway, are almost invariably involved in the involuntary movements characteristic of Parkinson's disease. Upper airway dysfunction is an important factor in the retained secretions, atelectasis, aspiration, and respiratory infection, which are frequently seen in patients with Parkinson's disease. Other potential complications include post-extubation laryngospasm and postoperative respiratory failure.<sup>4 21</sup> Sleep apnoea has been described in patients with post-encephalitic Parkinson's disease, but is now rarely seen.<sup>48</sup>

### *Autonomic nervous system*

Autonomic manifestations in patients with Parkinson's disease are rarely specific. Changes in various systemic

**Table 1** Recommended assessment of the patient with Parkinson's disease<sup>72</sup>

System	Assessment by history	Tests
Head and neck	Pharyngeal muscle dysfunction Dysphagia Sialorrhoea Blepharospasm	
Respiratory	Respiratory impairment from rigidity, bradykinesia or uncoordinated involuntary movement of the respiratory muscles	Chest x-ray  Pulmonary function tests Arterial blood gas analysis ECG
Cardiovascular	Orthostatic hypotension Cardiac arrhythmias Hypertension Hypovolaemia Autonomic dysfunction	
Gastrointestinal	Weight loss Poor nutrition Susceptibility to reflux	Serum albumin/transferrin Skin test anergy
Urological	Difficulty in micturition	
Endocrine	Abnormal glucose metabolism (selegiline)	Blood glucose concentration
Musculoskeletal	Muscle rigidity	
CNS	Muscle rigidity Akinesia Tremor Confusion Depression Hallucinations Speech impairment	

functions such as gastrointestinal, are common in old age and Parkinson's disease, and data on their relative frequency and severity are not available. Moreover, they may also be iatrogenic as a result of the side-effects of Parkinson's disease medication or other drugs. It is an unanswerable question whether an autonomic symptom is a manifestation of age, disease or therapy, or any combination of these factors. Patients with Parkinson's disease may complain of difficulty with salivation, micturition, and gastrointestinal function; some may also have defective cardiovascular control and temperature regulation. Seborrhoea, a classical feature of Parkinson's disease, is also an autonomic manifestation of the disease.<sup>51</sup>

### Cardiovascular system

Cardiac arrhythmias and dependent oedema may occur, but the most disabling symptom is orthostatic hypotension.<sup>36</sup> Postural hypotension was observed in patients before the start of L-DOPA therapy and was not associated with any abnormality of the cardiovascular response to a Valsalva manoeuvre. However, in evaluating orthostatic hypotension in patients with Parkinson's disease, the role of medication must be considered. Several drugs for Parkinson's disease may cause or exacerbate hypotension including L-DOPA acting through a central mechanism similar to alpha-methyl DOPA, although before the use of decarboxylase inhibitors peripheral conversion to dopamine also contributed to its

hypotensive effect. Direct-acting dopamine agonists, such as bromocriptine and lisuride, may precipitate hypotension by causing peripheral vasodilation. Finally, use of older antidepressants such as amitriptyline and other tricyclic antidepressants may cause orthostatic hypotension.

### Gastrointestinal function

Disturbances of gastrointestinal function are probably the most common autonomic features in Parkinson's disease. In his original monograph, James Parkinson wrote 'The power of conveying food to the mouth is at length so much impeded that he is obliged to be fed by others. The bowels, which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power. . .'.<sup>92</sup> Sialorrhoea is a common late manifestation of the disease but is probably due to reduced automatic swallowing and hence the poverty of motor movement rather than autonomic dysfunction. The amount of saliva produced is normal and the symptom responds to L-DOPA administration. However, the use of antimuscarinic drugs increases the viscosity of saliva and further impairs swallowing. The pathogenesis of dysphagia and abnormalities of oesophageal function is unclear. However, the discovery of Lewy bodies in the oesophageal myenteric plexus of a patient who had achalasia, but no extra pyramidal symptoms, may provide some clues.<sup>99</sup> Constipation and mild weight loss are also common.



## Anaesthesia in the patient with Parkinson's disease

### *General considerations*

The usual drug regimen should be administered as close to the beginning of anaesthesia as possible. L-DOPA can only be administered enterally and its half-life is short (1–3 h). It is absorbed from the proximal small bowel and, therefore, cannot be given as a suppository. Patients may self-administer additional L-DOPA, so it is important to find out exactly how much they are taking.<sup>106</sup> Furthermore, it is essential to ensure that patients do not miss medication doses postoperatively. Patients should be able to take L-DOPA either with sips of water or by nasogastric tube. Another strategy is to use subcutaneous administration of apomorphine. However, this is very emetogenic and patients usually need to take domperidone for several days before an apomorphine challenge. Nevertheless, small doses of apomorphine with sufficient antiemetic cover may be helpful.

Regional anaesthesia has obvious advantages over general anaesthesia as it avoids the effects of general anaesthetics and neuromuscular blocking drugs, which may mask tremor. If sedation is required, diphenhydramine has been described as useful particularly for ophthalmic procedures.<sup>121</sup> Its central anticholinergic activity is advantageous for patients with Parkinson's disease in whom tremor can render surgery difficult. With regional anaesthesia, postoperative nausea and vomiting, which may prevent resumption of oral intake, is also avoided. If general anaesthesia is required, it is worth noting that L-DOPA can be administered intraoperatively via a nasogastric tube.<sup>28</sup> Emergence from anaesthesia, even in healthy patients, is often marked by the transient appearance of a variety of what are otherwise considered to be pathological neurological reflexes, including hyperreactive stretch reflexes, ankle clonus, the Babinski reflex, and decerebrate posturing.<sup>112</sup> Shivering is common after general anaesthesia and regional analgesia and, again, should be distinguished from parkinsonian symptoms. Rigidity after both high-dose<sup>67</sup> and lower-dose<sup>17</sup> fentanyl is also well described in normal patients. Patients with Parkinson's disease are more prone to postoperative confusion and hallucinations.<sup>34</sup>

Drugs that precipitate or exacerbate Parkinson's disease should be avoided, including phenothiazines, butyrophenones (including droperidol), and metoclopramide. The latter may cause drug-induced Parkinson's disease. This is treated simply by drug withdrawal, but an obvious pitfall may be the misdiagnosis of idiopathic Parkinson's disease and administration of L-DOPA.<sup>3</sup> Potential drug interactions must also be considered. Patients on MAOIs have long been a specific concern of anaesthetists, but with the widespread use of selegiline, a MAOI-B type inhibitor, the likelihood of having to anaesthetize a patient receiving a

MAOI-A inhibitor is decreased. However, there are reports of agitation, muscle rigidity and hyperthermia in patients receiving meperidine and selegiline, so this combination should be avoided.<sup>140</sup> The use of potent non-steroidal anti-inflammatory agents has avoided the need for narcotic analgesics in patients on MAOIs undergoing relatively minor procedures.<sup>25</sup>

### *Inhalational anaesthetics*

Inhalational anaesthetic agents have complex effects on brain dopamine concentrations, inhibiting synaptic reuptake of dopamine, thereby increasing its extracellular concentration<sup>22</sup> and affecting both spontaneous and depolarization-evoked dopamine release.<sup>69</sup> These changes occur at clinically relevant concentrations of anaesthetic agents. For patients taking L-DOPA, anaesthetic agents such as halothane, which sensitizes the heart to the action of catecholamines, should be avoided. The newer inhalational agents, isoflurane and sevoflurane, are less arrhythmogenic, but hypotension is still a concern due to hypovolaemia, norepinephrine depletion, autonomic dysfunction and the co-administration of other medication. Patients taking bromocriptine or pergolide are prone to excessive vasodilation further exacerbating hypotension. Of historical interest, chronic trichloroethylene exposure has been implicated in the development of parkinsonism.<sup>37</sup>

### *Intravenous induction agents*

Previous case reports have described parkinsonian episodes in patients receiving thiopental,<sup>21 83</sup> and in animal studies thiopental decreased dopamine release from striatal synaptosomes.<sup>69</sup> The clinical significance of this is unclear and thiopental has not been directly implicated in exacerbating parkinsonian symptoms. Ketamine is theoretically contraindicated in Parkinson's disease because of an exaggerated sympathetic response, but it has been used in these patients without harm.<sup>40</sup> Recent interest has focused on the use of propofol in patients with Parkinson's disease, particularly those undergoing stereotactic pallidotomy or thalamotomy. Theoretically, propofol is an ideal agent to use while attaching the stereotactic frame, because of its rapid metabolism and emergence profile. Again, there is a paucity of evidence about its effects in patients with Parkinson's disease but case reports have described both dyskinetic effects,<sup>54</sup> and abolition of tremor,<sup>2</sup> in patients scheduled for stereotactic procedures leading to cancellation of surgery. As patients presenting for stereotactic surgery have their anti-parkinsonian medication stopped for 12–24 h preoperatively, so that their symptoms may be observed and then seen to be abolished, the second case report recommended that propofol is not used for these procedures because of its unpredictable effects.<sup>2</sup>

**Table 2** Possible drug interactions in patients with Parkinson's disease

Drug	Comments
<i>Induction agents</i>	
Propofol	Avoid for stereotactic procedures <sup>2 54</sup>
Etomidate	Probably safe
Thiopental	Probably safe
<i>Analgesics</i>	
Fentanyl	Possible muscle rigidity <sup>17 49 67</sup>
Meperidine	Avoid in patients on selegiline <sup>140</sup>
Morphine	Possible muscle rigidity <sup>9</sup>
Alfentanil	Possible dystonic reactions <sup>75</sup>
<i>Volatile agents</i>	
Isoflurane	Probably safe
Sevoflurane	Probably safe
Enflurane	Probably safe
Halothane	Possible arrhythmias
<i>Neuromuscular blocking drugs</i>	
Succinylcholine	Possible hyperkalaemia <sup>35 84</sup>
Non-depolarizing agents	Probably safe

### Neuromuscular blocking agents

There are no reported cases of non-depolarizing neuromuscular blocking drugs worsening the symptoms of Parkinson's disease. Succinylcholine has been reported to cause hyperkalaemia in a patient with Parkinson's disease,<sup>35</sup> although the case was complicated by other factors. A later case series looked at seven patients with Parkinson's disease, who received succinylcholine as part of their anaesthetic management and found no signs of succinylcholine-induced hyperkalaemia.<sup>84</sup>

### Opioids

There are numerous reports of muscle rigidity following the use of fentanyl in normal patients, and those with an established diagnosis of Parkinson's disease.<sup>49</sup> Opioid-induced muscle rigidity responds to neuromuscular block and is postulated to result from presynaptic inhibition of dopamine release.<sup>132</sup> Morphine has, however, also been shown to be associated with a reduction of dyskinesia at very low doses and an increase in akinesia at higher doses in patients with Parkinson's disease.<sup>9</sup> Acute dystonia after alfentanil has also been described,<sup>75</sup> and the severe interaction between meperidine and selegiline has already been noted.<sup>140</sup>

It is clear that there is no simple anaesthetic regimen for patients with Parkinson's disease. Much of the evidence about the safety of various anaesthetic drugs or techniques is based on single case reports or small case series. The absence of randomized controlled trials evaluating various anaesthetic techniques or drugs means that advice can only be based on data that have obvious limitations. What is apparent from these reports is that most patients with Parkinson's disease are elderly with coexisting medical conditions as well as the complications of the disease and its treatment. Meticulous preoperative assessment, maintenance of drug therapy up to the time of anaesthesia and afterwards, avoiding known precipitating agents and

intraoperative administration of L-DOPA if required, are key factors in the reduction of postoperative morbidity. These recommendations are summarized in Table 2.

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