

# MIND AND MOVEMENT: THE NEUROPSYCHIATRY OF MOVEMENT DISORDERS

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The irritating historical division between neurology and psychiatry is at its most arbitrary in the field of movement disorders. All of the major movement disorders (such as Parkinson's disease, idiopathic dystonia, Huntington's disease, and Gilles de la Tourette's syndrome) have important psychiatric dimensions; indeed these are often the primary determinants of quality of life. Similarly many of the major psychiatric disorders (such as schizophrenia and depression) involve abnormalities of movement, even though psychiatrists and neurologists have traditionally used different terms to describe them. Perhaps as a consequence of the historic division, these huge areas of neuropsychiatric overlap have not been studied as intensively as they deserve; in this review we aim to provide a pragmatic guide to management.

## PARKINSON'S DISEASE

### Depression

Depression is common in Parkinson's disease (PD), with a prevalence of about 30%. It is regarded by patients as one of the most unpleasant aspects of PD. It can occur at any stage of the disease, and occasionally may precede the onset of motor symptoms by a few years. In general, however, it becomes more common with increasing disease severity as assessed by the doctor, and increasing disability as assessed by the patient. People with PD who are depressed are also more prone to have anxiety disorders, psychotic symptoms or dementia.

Although the miseries of suffering from PD clearly contribute to the development of depression, it is best understood as a biological manifestation of the disease. Certainly PD is associated with pathology in all the brainstem monoaminergic nuclei, causing profound reductions in 5-HT (5-hydroxytryptamine) and noradrenaline (norepinephrine) concentrations. Depression is more common in PD than in other similarly disabling conditions. Neurologists must be proactive in looking for symptoms of depression: low mood, anhedonia, sleep disturbance, and a failure to feel better despite objective motor improvement are all potential pointers. They should trigger a detailed consideration of treatment rather than the traditional embarrassed murmurs of sympathy.

There have been remarkably few trials of antidepressant strategies in PD. Clinical experience suggests that there is a useful response to a wide range of antidepressant drugs. Tricyclics are best avoided in patients with cognitive impairment. Selective serotonin and selective noradrenaline reuptake inhibitors (SSRIs and SNRIs) are generally well tolerated and effective. There are theoretical reasons for preferring the SSRI sertraline (50–100 mg at night) as it is also weakly dopaminergic; the SNRI venlafaxine (37.5–75 mg twice daily) is sometimes better tolerated. Psychological approaches, such as cognitive behavioural therapy, may also have a place.

People with PD whose motor condition fluctuates widely often also experience distressing swings in their mental state. For example, "off" periods may be accompanied by intense feelings of doom or dread. Patients naturally respond to this by over-medicating and come to clinic in a dyskinetic state. Again SSRIs or SNRIs may be a very helpful adjunct to the normal strategies for managing fluctuations or dyskinesia.

### Anxiety

Anxiety disorders are probably just as common but have received less academic scrutiny. Generalised anxiety and panic attacks associated with "off" periods are common. Social phobia seems to be particularly under recognised. Again these are gratifying conditions to recognise and treat, responding either to drugs (as above) or psychological therapy (for example, through a PD specialist nurse) or both, with dramatic improvements in quality of life for all concerned. Support from the local group of the Parkinson's Disease Society may also be invaluable.

### Psychosis

Psychosis in PD most commonly takes the form of complex visual hallucinations, typically of recognisable living things, which may talk to the patient. Auditory hallucinations occurring in the absence of visual hallucination are rare. There may be accompanying paranoid ideation. In younger patients the psychosis is usually drug induced or secondary to depression. In older patients it is

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usually a harbinger of dementia, but again may be secondary to depression. It follows that in either age group, a careful enquiry for symptoms of depression, and often a trial of treatment, is a vital first step.

In either age group it is traditional to reduce or withdraw drugs that may be causing or exacerbating the psychosis. Benzhexol (or other anticholinergics) is a particular culprit in older patients and should be slowly withdrawn first, followed by drugs like selegiline and amantadine which may be relatively less important in controlling the parkinsonism anyway. Often one has to accept the return of tremor or dyskinesia as the price for an improvement in mental state. In younger patients the dopamine agonists are usually the problem. Again a gradual dose reduction may relieve the psychosis at the expense of a worsening of PD; it may then be possible to retrieve this situation by moving towards apomorphine (the dopamine agonist with the least tendency to cause psychosis) or by adding levodopa.

There are two alternative strategies that should be considered once depression has been excluded and drug treatment has been simplified as far as possible. The first is to suppress psychosis with an atypical neuroleptic. This works best in younger patients who are cognitively intact. Clozapine is the drug with the least scanty evidence base, but requires burdensome haematological monitoring. Quetiapine seems to be less potent, but is certainly more convenient. It should be started slowly if possible (for example, 25 mg at night) but does not usually help until large doses are achieved (for example, 200 mg twice daily). Olanzapine can also be helpful but carries greater risk of exacerbating parkinsonism or causing confusion. None of these drugs is very sedating, so when sedation is required the options are to add a benzodiazepine or alternatively use very small doses of sulpiride. Sulpiride almost always causes some deterioration of parkinsonism.

A second strategy for treating psychosis, which works best in patients with cognitive impairment, is to use cholinesterase inhibitors. These drugs, which are licensed and endorsed by the National Institute for Clinical Evidence for the treatment of Alzheimer's disease, have if anything a greater effect in treating the psychosis or dementia associated with PD. This presumably reflects the fact that cholinergic deficits are more profound in PD. The evidence base is again scanty, with no randomised controlled studies and a single excellent study in the related condition of dementia with Lewy bodies (see below). Clinical experience suggests that rivastigmine, donepezil, and galantamine may all have useful antipsychotic effects in people with PD who have cognitive impairment. There are no studies of comparative potency in this setting. Rivastigmine (1.5 mg twice daily increasing slowly to 6 mg twice daily) is the drug that has been shown to be useful in dementia with Lewy bodies. Donepezil (5 mg once daily increasing to 10 mg once daily) has the simplest titration schedule and is possibly the most potent of the three drugs when used in Alzheimer's disease. Diarrhoea, which often causes problems in Alzheimer patients, is rarely a problem in PD, but agitation and motor restlessness may occur.

### Dementia

Dementia itself is the most serious neuropsychiatric complication of PD, affecting about 30% of patients, usually after the age of 65 years. Psychosis, especially visual hallucination, is often the presenting symptom. Cognitive function may fluctuate and be accompanied by periods of frank confusion. Episodic memory is usually poor (but occasionally surprisingly preserved). Frontal lobe function, which is abnormal in

### Abbreviations

**HD:** Huntington's disease  
**OCD:** obsessive compulsive disorder  
**PD:** Parkinson's disease  
**SSRI:** selective serotonin reuptake inhibitor  
**SNRI:** selective noradrenaline reuptake inhibitor  
**TS:** Tourette's syndrome

many non-demented people with PD, declines further, often manifesting as an increase in apathy and inertia. Visuospatial function also declines early on, and this can be conveniently detected in the clinic setting by clock drawing. Gradually a global dementia emerges.

The usual pathological correlates of this are large numbers of cortical Lewy bodies and primitive senile plaques, although some cases have pathology typical of Alzheimer disease (with tau-containing neurofibrillary tangles and neuritic plaques). The distinction between dementia in PD and dementia with Lewy bodies is, therefore, semantic rather than biological in most cases. In practice this means that a trial of cholinesterase inhibitors is worth considering. The recent study of McKeith and colleagues<sup>1</sup> looked at patients with dementia with Lewy bodies, excluding by definition patients whose parkinsonism preceded their dementia by more than a year. About half of this group of patients showed a clinically useful response, with a suppression of psychosis and fluctuations, and improvements in cognitive processing. Our experience is very similar in PD with dementia.

### HUNTINGTON'S DISEASE

It is well known that Huntington's disease (HD) can present with neuropsychiatric symptoms, including depression, psychosis, obsessive compulsive disorder (OCD), and a frontal lobe syndrome with either disinhibition, impulsivity, and aggression or apathy and self neglect. A tendency to present in one of these ways may run within individual families. Initial treatment of these symptoms may involve a neuroleptic, which then suppresses chorea and makes diagnosis difficult. The most extreme example of this that we have encountered was a middle aged woman who had been treated for several years for a delusional disorder in which she believed that she was a witch. It was only when neuroleptics provoked unexpectedly severe parkinsonism, and the strong family history of psychiatric disorder and suicide was reconsidered, that the diagnosis of HD emerged.

Suicide remains a major concern in HD, both because of its neuropsychiatric manifestations (with the combination of depression and impulsivity representing a particular risk) and because most patients know, by virtue of their family history, what their future holds. Psychological support, from genetic counsellors, specialist multidisciplinary HD clinics, and the Huntington's Disease Association, is vital. As in PD, the broadening range of drug treatments has also helped. Antidepressants are the most commonly prescribed drugs in most HD clinics. SSRIs are usually helpful in treating depression or OCD (or both); they occasionally exacerbate chorea in which case low dose flupenthixol is an alternative. The main problem with using neuroleptics is their tendency to accelerate the natural switch that HD patients make from chorea to parkinsonism and dystonia. As with PD, atypical neuroleptics allow psychosis to be treated with fewer motor complications.

## MOVEMENT DISORDERS IN “PRIMARY PSYCHIATRIC DISEASE”

### Depression

Depression is often accompanied by a phenomenon termed psychomotor retardation by psychiatrists. This retardation is a core feature of major depressive disorder, indicating a more severe disorder with a poorer prognosis. The retardation can be so severe that patients can die from dehydration or starvation, or from suicide during a burst of agitation. To a neurologist retardation is the same phenomenon as bradykinesia. This view is reinforced by studies of psychomotor function and reaction times showing no difference between depressed patients and PD patients in these measures.<sup>2</sup>

### Obsessive compulsive disorder and Tourette’s syndrome

OCD is often associated with disorders of movement. The most obvious example of this, and indeed the condition that best illustrates the overlap between neurological and psychiatric manifestations, is Gilles de la Tourette’s syndrome (TS). TS is defined on the basis of its movement disorder, with multiple motor and phonic tics, but the accompanying OCD is often the principal source of disability. The phenomenology of OCD in TS is very similar to that of isolated OCD, with complex rituals and complex checking; repetitive hand washing is less common. First degree relatives of TS patients may have isolated OCD without a movement disorder. Conversely, patients with apparently isolated OCD have an increased frequency of mild tics. This would all suggest that OCD and TS may share a common biological substrate. Functional imaging studies have produced complex and sometimes conflicting results, but raise the possibility that this substrate may involve abnormal connectivity between the basal ganglia and prefrontal cortex.

### Schizophrenia

Schizophrenia has been known to involve movement disorder since Kraepelin’s classical descriptions in the 19th century. The most florid manifestation of this is catatonia, a subsyndrome affecting up to 10% of those with schizophrenia. Patients present with schizophrenic symptoms, classically delusions, thought disorder, and auditory verbal hallucinations, but also have prominent abnormality of movement. They either display a reduced level of spontaneous movement with mutism, or excitability with increased level of apparently purposeless activity, or frequently a combination of the two, with periods of mutism punctuated by bursts of excitement. They may also show posturing (where a bizarre or uncomfortable position is held for lengths of time), negativism (with resistance to instructions or attempts to move), command automatism (with automatic obedience to tasks), or waxy flexibility (where patients can be moved into positions which they will then maintain.) Catatonia is not confined to schizophrenia, and is occasionally seen in mania or in association with a confusional state of whatever aetiology.

The treatment of catatonia is distinct from other forms of schizophrenia, which indicates perhaps a separate aetiology. Antipsychotic medications can worsen the disorder. Benzodiazepines and electroconvulsive therapy are both effective and indeed lifesaving in some cases. The efficacy of these treatments raises the possibility that the pathophysiology relates to an abnormality of GABA ( $\gamma$  aminobutyric acid) circuitry, causing a failure of central motor inhibition.

The chronic stage of a schizophrenia illness is characterised by a progression from the early symptoms of hallucinations,

thought disorder and delusional beliefs to so-called negative symptoms. These include psychomotor slowing, passivity and lack of initiative, poverty of facial expression or voice modulation, and poor social performance. Again these features show phenomenological similarities with those seen in parkinsonian disorders. This stage of illness is particularly difficult to treat, although newer, atypical antipsychotics such as risperidone, olanzapine or clozapine are possibly more effective. It is important to distinguish negative symptoms from other causes of similar symptoms such as depression or parkinsonian side effects of medication.

Other movement disorders are also seen as part of the syndrome of schizophrenia. These include manneristic behaviour, with repeated semi-purposeful movements, stereotypies such as rocking to and fro, echopraxia where gestures are imitated repetitively, and ambivalence with alternation between opposite movements such as hovering to and fro in a doorway.

## MOVEMENT DISORDERS AS SIDE EFFECTS OF PSYCHIATRIC MEDICATION

Dystonia, akathisia, parkinsonism, and choreiform dyskinesia are common side effects of antipsychotic medications. They are distressing to the patient, and contribute to the stigmatisation of psychiatric illness, by making patients visibly different. They are also a key reason for non-compliance with treatment. Although originally associated with classical antipsychotic agents such as chlorpromazine or haloperidol, they have also been described in association with a wide range of other psychotropic drugs, including all the atypical neuroleptics, antidepressants (both tricyclic and SSRI,) and anticonvulsants such as sodium valproate.

Acute dystonias, usually of the face or neck, can occur within 72 hours of starting a new medication. They are particularly common with haloperidol, occurring in up to 10% of cases, but can occur with other antipsychotics. They are quickly treatable with anticholinergic agents, and withdrawal of the offending agent.

Tardive movement disorders are much more difficult to treat. The most common is orofacial dyskinesia, provoked by long term neuroleptic treatment and persisting (or worsening) after this is withdrawn. It usually manifests as choreoathetoid movements of the tongue and lower face, although any body area can be involved, including pharyngeal and intercostal muscles. It is particularly common in elderly patients, women, and those who have been on long term treatment (more than 10 years) at higher doses, occurring in up to 50% of these patients.<sup>3</sup> However, it has become clear recently that tardive dyskinesia can also occur as a result of the schizophrenic illness itself, being seen in up to 15% of drug naïve persons. A similar phenomenon is also seen in elderly people with no psychiatric disorder, especially edentulous women with minor cerebral vascular disease on brain imaging. It has been postulated that tardive dyskinesia occurs as a result of an imbalance of D1/D2 dopamine receptors within the basal ganglia. The standard approach to treatment is to reduce and stop the antipsychotic treatment if possible, substituting with clozapine if necessary. Clozapine is the only drug that has been shown to improve tardive dyskinesia once established. There is little evidence to support the use of any other agents, although a huge number of drugs have been tried.<sup>4</sup>

Akathisia is a common and distressing form of motor restlessness, occurring in a quarter of patients with chronic schizophrenia in one study.<sup>5</sup> Again it is particularly associated

with high potency antipsychotics such as haloperidol. If it occurs early in treatment, reducing or stopping the medication responsible can usually improve it, but if it occurs more chronically it is often resistant to these measures.

Drug induced parkinsonism is a common side effect of antipsychotic medication, and is sometimes clinically indistinguishable from PD. Drug induced parkinsonism is more likely to be symmetrical and rarely, if ever, gives rise to a classical resting tremor. It is, of course, possible to have both drug induced parkinsonism and PD. It is possible that relatively straightforward forms of functional brain imaging, such as DAT scanning (using a dopamine transporter ligand) will help in making these distinctions. Drug induced parkinsonism is especially common in elderly patients, and in those on high dose dopamine blocking medication. Positron emission tomography studies of D2 receptor blockade show that parkinsonism develops when D2 occupancy exceeds 80%, a 70% occupancy being sufficient for an antipsychotic effect. The therapeutic window is thus narrow, but if the patient displays parkinsonism they are being overtreated, and it should be possible to titrate a dose that treats the illness without inducing parkinsonism. Anticholinergic drugs are also often used to treat parkinsonism, but carry the risk of reducing the efficacy of the antipsychotic agent, causing a confusional state and possibly increasing the risk of tardive dyskinesia. It is not, therefore, good practice to prescribe these drugs long term.

### NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome is a potentially life threatening reaction to antipsychotic medication. It is characterised by altered consciousness, muscle rigidity, fever, and autonomic instability. Muscle rigidity may cause dyspnoea and dysphagia. The response appears to be idiosyncratic with no particularly susceptible patient group. It has also been described following administration of a wide variety of drugs, but particularly those with potent D2 blockade such as haloperidol. Treatment is supportive, maintaining fluid balance,

### Key points

- ▶ Movement disorders have an important psychiatric dimension that warrants careful enquiry, and can lead to difficulties in treatment
- ▶ Psychiatric disorders have associated disorders of movement, which require specific treatment strategies
- ▶ Psychoactive medications have movement disorders as side effects, both in the short and longer term, which require consideration when prescribing

cooling the patient, and ventilating if necessary. Muscle relaxants are usually used, in an attempt to reduce fever and rhabdomyolysis caused by continuous muscle contraction. The offending drug should be stopped. There is some support for the use of dopamine agonists in treatment, the theory being that neuroleptic malignant syndrome occurs as a result of central blockade and down regulation of D2 receptors. Once the patient has recovered it is conventional to restart treatment, where necessary, with a neuroleptic drug from a different class. However, there are cases where the same drug has been reintroduced a few weeks later without problems, highlighting the idiosyncratic nature of this syndrome.

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