

4 Mental Health Disorders in Parkinson's Disease

Dr G Lennox

Consultant Neurologist, Department of Neurology, Great Western Hospital, Swindon

Neuropsychiatric symptoms are common in Parkinson's disease (PD) and make a major impact on quality of life for patients and carers. Broadly speaking, in the early years of PD the most common problems are anxiety, depression and apathy. In more established disease, psychosis and impulse control disorders come to the fore. Later, dementia becomes the dominant problem for the majority of patients.

Anxiety and Depression

Many patients, presenting for the first time with motor symptoms of PD, describe a pro-drome of increasing anxiety or depression. Developing depression for the first time in mid-life is in fact a measurable risk factor for going on to get PD, increasing the chances of this threefold. In established PD, the prevalence of anxiety and depression is about 30%.

These problems can be over-looked, or dismissed as an understandable reaction to the diagnosis of PD. They are important to recognise, and not just because of the obvious negative emotional impact: anxious patients are more likely to over-medicate (especially when anxiety occurs during wearing-off) and depressed patients tend to have an impaired motor response to medication, as well as an increased risk of other neuropsychiatric problems such as impulse control disorders and cognitive impairment.

It is important (and easy) to screen for these problems. Movement disorder specialists are often comfortable in looking for signs of anxiety and depression, but this is no substitute for a simple screening question like, "Are you feeling cheerful and relaxed?" The core symptoms of depression in PD are low mood and anhedonia (i.e. loss of enjoyment of normally-pleasurable activities); impaired libido and sleep disturbance are also common.

Both anxiety and depression tend to respond to antidepressant treatment. In the case of depression, this is now evidence-based, with the largest and longest study, SAD-PD, showing that both paroxetine (an SSRI) and venlafaxine (an SNRI) were superior to placebo over 12 weeks of treatment.¹ Cognitive behavioural therapy has also been shown to be superior to clinical monitoring, with more than 50% of patients achieving a predefined treatment response over 10 weeks of therapy.

Apathy

Apathy, manifest as a loss of motivation and drive, and often accompanied by indecisiveness, is another common early symptom of PD.² Apathy can also cause anhedonia and differs from depression in that there is no lowering of mood (unless the patient has both apathy and depression, which is common.) It can be particularly troublesome to younger patients who are still working, and to the families of patients of any age. It is associated with cognitive deficits of a frontal executive type, which may in turn have a genetic basis (with, for example, an association with particular COMT polymorphisms). It is also associated with depression but can occur independently and then does not respond to antidepressant treatments. Basic science research suggests dopaminergic, noradrenergic or cholinergic drugs may potentially be of benefit, and a randomised controlled trial supports the use of rivastigmine (in non-depressed, non-demented patients).³ Pragmatic approaches rely on establishing a system of external motivation, through regular routines and an enthusiastic partner.

Psychosis

Psychosis occurs in patients who have had PD for a few years and is surprisingly common. Mild forms are reported by about 25% of patients, again often in association with depression and/or sleep disturbance. These include illusions of presence (where the patient feels that there is someone in the room with them when there is not) and mild visual hallucinations (sometimes little more than misperceptions, where a real object like a dressing gown hanging on the bedroom door is briefly thought to be an intruder).

Visual hallucinations can become much more florid, with complex and persistent images of people (often distorted, small with big heads) or animals, or less commonly patterns and grids. Such hallucinations are often accompanied by hallucinations in other modalities (for example hearing the people talk or feeling them sitting on the bed) and by delusions. These more severe psychotic phenomena can purely reflect excessive anticholinergic or dopaminergic medication, or inter-current illness such as infection, but unfortunately mainly occur in the context of cognitive impairment and are a harbinger of dementia.

If there has been a recent increase in PD medication, then the psychosis can sometimes be managed by reversing this. Inter-current illness and sleep disturbance should be treated where possible. In most cases, however, and especially if there is accompanying cognitive impairment, the best strategy is to introduce a cholinesterase inhibitor such as rivastigmine⁴. It is encouraging to see the recent studies suggesting that the 5HT_{2A} inverse agonist pimavanserin may be an effective anti-psychotic drug in PD, in what is the first attempt to develop a treatment specifically for a neuropsychiatric manifestation of PD.⁵

Impulse Control Disorders and DAWS

Impulse control disorders (ICDs) are a feature of established PD, typically in patients taking a dopamine agonist, usually in combination with levodopa. Clinically significant ICDs probably affect at least 20% of patients. They take a very wide range of forms, from over-eating and spending, through excessive pursuit of hobbies and purposeless messing around ('punding'), to very distressing behaviours like over-medicating ('dopamine dysregulation syndrome'), risk-taking, gambling and disinhibited sexual activity of all kinds. Patients often have more than one ICD. The typical high-risk patient for ICD has premorbid impulsive traits (such as a previous addiction) or a family history of this, has developed PD at a young age, is depressed, and is striving for perfect motor control by taking a lot of medication.

The keys to managing ICDs are prevention (asking all patients and their families to report unusual behaviour changes and negotiating lower treatment goals in those with risk factors for ICDs) and screening for ICDs at review visits; patients find ICDs embarrassing and may be very reluctant to disclose them, even when directly asked.

ICDs will usually disappear with reduction in dopamine agonist dose (or a switch from more potent pramipexole or ropinirole to less potent rotigotine). This often requires a compensatory increase in levodopa, or even consideration of DBS. Abrupt discontinuation of dopamine agonists can result in Dopamine Agonist Withdrawal Syndrome (DAWS), a recently described combination of anxiety, depression, sweating and craving for the missing agonist. It is not yet clear if this really is a distinct entity and, if so, whether it should be treated symptomatically or by a partial reintroduction of the missing agonist followed by a more gradual withdrawal.

Dementia

Dementia is the most serious and most feared complication of Parkinson's disease. Community-based studies have shown a cumulative incidence in patients who have survived for 8 years with PD of 65-80%. Typically, dementia starts in patients who are more than 75 years old (regardless of the duration of PD), especially if they have a postural instability-gait disturbance phenotype or other risk factors for dementia (such as vascular risk factors). Genetic factors such as tau haplotype are also important.

Early symptoms include the visual hallucinations already discussed, daytime drowsiness and fluctuating cognitive impairment. The cognitive symptoms are typically attentional to begin with, and later progress to impairments of memory, visuospatial ability and language. Frontal-executive dysfunction also tends to be prominent (and more severe in relation to the overall level of dementia than in Alzheimer's disease.)

Although it is rare to find an alternative explanation in a patient with typical symptoms of this kind, it is sensible to check a dementia screen of routine blood tests and a CT or MR brain scan to rule out other more treatable pathology. The combination of dementia and movement disorder is associated

with very high levels of carer burden and a high mortality rate. Cholinesterase inhibitors and memantine may be of some benefit although this effect is rarely sustained for more than a year or two.

This makes prevention important, and there have been interesting studies suggesting that exercise, social engagement, cognitive training and control of vascular risk factors may all have a role to play. But ideally, we need a neuroprotective treatment for PD that prevents its dementia⁶. Randomised controlled trials of potential neuroprotective drugs like exenatide⁷ are awaited with great interest.

References

1. Richard IH et al. A randomised, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. *Neurology* 2012; 78: 1229-36.
2. Pagonabarraga J et al. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis and treatment. *Lancet Neurol* 2015; 14: 518-31
3. Devos D et al. Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial. *J Neurol Neurosurg Psychiatry*. 2014 Jun;85(6):668-74.
4. Rolinski M et al. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. *Cochrane Database Syst Rev* 2012 Mar 14;3:CD006504. doi: 10.1002/14651858.CD006504.pub2.
5. Cummings J et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet* 2014; 383: 533-40.
6. Athuada D, Foltynie T. The ongoing pursuit of neuroprotective therapies in Parkinson disease. *Nat Rev Neurol* 2015; 11: 25-40.
7. Aviles-Olmos I et al. Motor and cognitive advantages persist 12 months after exenatide exposure in Parkinson's disease. *J Parkinsons Dis* 2014; 4: 337-44

Further Reading

Connolly B, Fox SH. Treatment of cognitive, psychiatric, and affective disorders associated with Parkinson's disease. *Neurotherapeutics*. 2014 Jan;11(1):78-91.

Goldman JG, Holden S. Treatment of psychosis and dementia in Parkinson's disease. *Curr Treat Options Neurol*. 2014 Mar; 16(3): 281.

Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, Hametner EM, Poewe W, Rascol O, Goetz CG, Sampaio C. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. *Mov Disord*. 2011 Oct; 26 Suppl 3: S42-80.