



Management of the neuropsychiatric and

INTRODUCTION

Neuropsychiatric and cognitive symptoms – depression, anxiety, psychosis and dementia – are common in Parkinson's Disease (PD) (Table 1). Moreover, they are frequently a major source of distress, both to patients and their families, and can be even more debilitating than the motor problems. Indeed, their presence, particularly dementia and psychosis, is an important predictor of nursing home placement.

Neuropsychiatric and cognitive symptoms in PD may occur because of the underlying pathological changes in the brain, drug treatment, or concurrent illnesses. There are significant dopaminergic and other neurotransmitter deficiencies in the frontal and limbic areas in PD, which may cause neuropsychiatric and cognitive problems. Whilst dopaminomimetic agents improve motor symptoms, they may also stimulate dopaminergic receptors in the frontal and limbic areas, resulting in psychotic symptoms. Other drugs such as anticholinergics can cause confusion or amnesia. Co-morbid conditions and diseases may also impair cognitive function and behaviour.

While dementia is difficult to treat, depression, anxiety, and psychosis often respond well to therapeutic interventions and are therefore particularly important to detect.

Table 1 Neuropsychiatric and cognitive symptoms in Parkinson's disease

Agitation
Anxiety and panic disorders
Depression
Sleep-wake cycle and sleep disturbances
Psychosis (hallucinations, delusions)
Confusion
Cognitive impairment (dysexecutive syndrome)
Dementia

DEPRESSION

Depression is one of the most frequent neuropsychiatric symptoms encountered in PD and can lead to even more disability and a greater risk of morbidity and mortality. The prevalence ranges from 4% to 90% in different studies. About 40% of patients suffer from depression at least once during the course of their disease (Cummings 1992). Depression can even occur before the onset of motor symptoms in up to 43% of patients (Santamaria *et al.* 1986).

There are several risk factors for the development of depression but these are not consistent across studies: early onset of PD (before the age of 55), disease duration, illness severity, bradykinesia, gait instability, family history, past history of depression, high levels of anxiety and female gender. Depression may be related to the rapid progression of PD and perhaps to accelerated cognitive decline (Tröster *et al.* 1995).

The clinical features of depression in PD span a broad range of symptoms from mild dysthymia to disabling major affective disorder. Depression in PD is distinguished from other depressive disorders by greater anxiety and panic and by the relative lack of self-reproach, guilt and suicidal ideation with rare actual suicidal behaviour. In some patients, mood changes occur during motor fluctuations, patients becoming depressed or agitated during the 'off' state.

The diagnosis of depression in PD can be difficult because of the overlap between depressive features and the symptoms of PD itself. Disturbed emotional processing, psychomotor retardation, attention deficit, day-night sleep reversal, hypophonia, bradyphrenia, impotence, insomnia, weight loss, fatigue, bradykinesia, preoccupation with health, and reduced facial expression are seen in both conditions.

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Practical Neurology 2002, 2, 94–102

and cognitive symptoms in *Parkinson's Disease*

Depression in PD may be due to the underlying disease process, reactive to having chronic motor disability, or both. The cause of endogenous depression in PD remains uncertain. Biochemical studies suggest that it may be the result of dysfunction of mesolimbic-cortical dopaminergic projections and relative deficiency of monoamines (serotonin and noradrenalin). CSF levels of 5-hydroxyindolacetic acid (5-HIAA), the major metabolite of serotonin, are significantly depressed (Mayeux *et al.* 1984). In addition, postmortem studies in depressed patients with PD have revealed extensive cell loss in locus ceruleous and dorsal raphe nucleus (Paulus & Jellinger 1991).

Management

The recognition and effective treatment of depression in PD improves quality of life, cognition, and mobility (Table 2). An attempt to reduce any environmental stress is the first step. If counselling alone is ineffective, depression must be treated aggressively. Supportive psychotherapy should principally be added to drug treatment.

Table 2 The stepwise approach to the management of depression in Parkinson's disease

Reduce environmental stress if practical
Maximize motor function with levodopa or dopamine agonists
Add a selective serotonin re-uptake inhibitor (SSRI)
Consider tricyclic or other antidepressants if SSRI not tolerated or ineffective
Perhaps ECT if severe drug resistant depression

There have been various therapeutic attempts to treat depression in PD, but only a few small double-blind studies. Levodopa, dopamine agonists, monoamine-oxidase (MAO) inhibitors, tricyclic antidepressants, selective serotonin re-uptake inhibitors and electroconvulsive therapy have all been tried (Cummings & Masterman 1999). The choice depends on the presence of comorbid medical conditions, interaction with concomitant PD medication, and the adverse effect profile of the antidepressant. Treatment of PD so often involves multiple drugs, which increases the risk of adverse drug-drug interactions.

The half-life of many antidepressants increases with age and dose reduction may be necessary when treating elderly patients. All antidepressants should be started at the lowest possible dose and gradually increased as necessary (Table 3). The treatment must be

maintained for at least 2 weeks before any improvement can be expected. Antidepressants should be continued for at least 6 months if they seem to be working.

Levodopa and dopamine agonists

Levodopa and dopamine agonists may improve depression in PD. Levodopa treatment seems to have only a brief beneficial effect, presumably due to the amelioration of motor symptoms. Dopamine agonists may ameliorate depressive symptoms when given as adjunctive treatment, or alone. Therefore, in patients with mild depressive symptoms and who also need improvement of their motor symptoms, a dopamine agonist may be considered first. Among antidepressant drugs, only bupropion has substantial dopaminergic properties by blocking dopamine uptake, and it improves mood in depressed PD patients (Goetz *et al.* 1984).

Selective serotonin reuptake inhibitors

The medical treatment of depression in PD is usually initiated with selective serotonin re-uptake inhibitors (SSRIs) because they are tolerated better, particularly in the elderly, and are possibly more effective than either tricyclics or MAO inhibitors. In open-label studies, fluvoxamine, fluoxetine, citalopram, paroxetine and sertraline were effective (Ceravolo *et al.* 2000; Dell'Agnello *et al.* 2001). SSRIs do, however, increase central dopaminergic activity, which may inhibit dopamine release from dopaminergic neurones, and there have been several case reports suggesting they can worsen motor function in patients with PD – this improves after drug withdrawal (Jansen Steur 1993). This effect has not been confirmed in the small number of open-label studies and generally does not restrict the use of SSRIs in PD. Avoiding rapid titration and high doses, and early recognition of worsening in motor function may reduce any potential risks.

The common adverse effects include nausea, diarrhoea, constipation, anxiety, restlessness, akathasia, insomnia, sedation, weight change, anorexia, increased sweating, postural hypotension, postural tremor, dizziness, dry mouth, allergic reactions, delayed ejaculation and impotence in men and anorgasmia in women. Should agitation already exist, caution must be exercised because of potential exacerbation with SSRIs. This effect may be desirable in patients who are drowsy or apathetic, but it is

Drugs	Daily dose (mg/day)*
<i>Serotonin reuptake inhibitors</i>	
Fluvoxamine	100–300
Fluoxetine	20–80
Citalopram	20–60
Paroxetine	10–40
Sertraline	50–200
<i>Tricyclic antidepressants</i>	
Amitriptyline	50–300
Nortriptyline	50–150
Desimipramine	75–300
Imipramine	50–300
Doxepine	50–300
Maprotiline	75–225
<i>Monoamine oxidase-A inhibitors</i>	
Moclobemide	150–600
<i>Others</i>	
Trazodone	200–600
Bupropion	200–450
Venlafaxine	75–375
Mirtazapine	15–45
Nefazodone	200–600
Reboxetine	4–10

*Always start with low doses and gradually work up to the 'therapeutic' dose listed here.

Table 3 Drugs for depression in Parkinson's disease and daily therapeutic doses

All antidepressants should be started at the lowest possible dose and gradually increased as necessary

undesirable in agitated patients. SSRIs should initially be given in the morning to minimize the risk of insomnia.

Tricyclic antidepressants

If SSRIs are ineffective or not tolerated, tricyclic antidepressants (TCAs; amitriptyline, nortriptyline, desimipramine, imipramine) are the second choice. Classical TCAs inhibit the uptake of noradrenaline, serotonin and some also of dopamine, in addition they block muscarinic and H₁-histaminergic receptors. TCAs do not induce parkinsonism and may ameliorate motor symptoms, particularly tremor, although desimipramine has been reported to aggravate tremor.

The common adverse effects include anticholinergic (dry mouth, constipation, urinary retention, paralytic ileus, acute glaucoma, blurred vision, confusion, memory and cognitive impairment), antihistaminergic (excessive sedation) and antiadrenergic effects (postural hypotension, tachycardia and anxiety). Anticholinergic activity can help to reduce any urinary frequency or sialorrhoea, but because of other potential adverse effects their use in

elderly patients is restricted. Nortriptyline and desimipramine have less anticholinergic activity than the others. TCAs may sometimes be used to avoid the agitation caused by SSRIs. They also have sedative properties, which can be detrimental for apathetic patients, but beneficial for those with anxiety or insomnia. Occasionally, paradoxical responses, such as increased anxiety, restlessness and insomnia, may occur.

Monoamine oxidase (MAO) inhibitors

Deprenyl, a selective inhibitor of MAO-B, has antidepressant activity in animals, but no clinically meaningful antidepressant activity has been shown in man. Moclobemide is a potent, reversible MAO-A inhibitor, and had antidepressant effects in patients with PD in an open-label study, comparable to SSRIs (Gimenez-Roldan *et al.* 1997). However, MAO inhibitors should be discontinued 2 weeks before starting any other antidepressant treatment because of the risk of the serotonin syndrome. Although this syndrome is extremely rare, it is potentially fatal, with autonomic and cardiovascular instability.

Electroconvulsive therapy

In patients with severe depression refractory to antidepressants, electroconvulsive therapy (ECT) can be considered and it may also improve motor function, particularly rigidity (Douyon *et al.* 1989). Motor improvement usually precedes improvement in mood and can last from days to weeks. ECT is usually given two to three times per week for 6–12 treatments. The adverse effects are mainly memory dysfunction and transient confusion that last several weeks. Headache and nausea are also frequent, but are transient and responsive to mild analgesic and anti-nausea drugs. ECT has been reported to improve drug-induced psychosis in PD patients.

Other compounds

In open trials and case reports, 5-hydroxytryptophan, reboxetine (selective noradrenaline reuptake inhibitor), and S-adenosyl methionine have all been reported to be effective in depressed patients with PD. Newer antidepressants such as venlafaxine (norepinephrine-serotonin reuptake inhibitor), nefazodone (combined serotonin reuptake inhibition with serotonin 5-HT₂ receptor antagonism) and mirtazapine (serotonin-noradrenaline reuptake inhibitor) have favourable pharmacokinetic profiles and may be effective in depression associated with PD, but none have been formally tested.

ANXIETY DISORDERS

Generalized anxiety, agitation, panic attacks and phobic disorders are all common occurring in up to 40% of PD patients (Walsh & Bennett 2001). Depression may or may not be present also and can worsen the symptoms of anxiety. Anxiety disorders may worsen motor symptoms of PD, while anxiety or panic attacks can be exacerbated with antiparkinsonian drugs or motor complications such as drug-induced dyskinesias and 'on-off' phenomena. Anxiety disorders may be a secondary reaction to the illness or related to neurochemical changes in the brainstem dopaminergic, noradrenergic, or serotonergic neurones.

Management

The first step is to gradually reduce or discontinue drugs with anxiogenic potential (such as anticholinergics, selegiline, amantadine, and dopamine agonists), if possible. Levodopa

dose can be reduced in an attempt to decrease agitation or anxiety, but this may worsen motor performance. The optimal pharmacological treatment of anxiety in patients with PD is not well-established, but benzodiazepines are the most commonly-used drugs. Should patients suffer from persistent anxiety low doses of short-acting anxiolytics may be effective. The short-acting benzodiazepines alprazolam (0.5–1 mg t.d.s.), lorazepam (0.5–2 mg t.d.s.) and diazepam (2–5 mg t.d.s.) are the preferred drugs. They are initially used on an 'as per need' basis, rather than regularly. Unfortunately, benzodiazepines may be poorly-tolerated and induce or worsen confusion, or worsen motor performance in older and cognitively impaired patients. Therefore, minimal doses are suggested. When discontinuing, they should be tapered over a 2 week period to avoid withdrawal effects. Buspirone may be effective to treat anxiety, but can block dopaminergic transmission. If patients with anxiety do not respond to benzodiazepines and other therapeutic interventions, the anxiety might be a manifestation of depression and so treatment with an SSRI or tricyclic with minimal anticholinergic and moderate sedative activity should be tried. If symptoms of anxiety emerge during 'off' periods, treatment of motor fluctuations can relieve the problem.

PSYCHOSIS

Psychosis is the most disturbing and disabling neuropsychiatric symptom in PD, occurring in 15–25% of patients on chronic dopaminergic treatment. Mild symptoms such as vivid dreams and illusions are reported more frequently (up to 50%). Psychosis is a major risk factor for permanent nursing home placement and is associated with a high mortality. At times it can be more disabling than the motor dysfunction. Psychosis before the initiation of dopaminergic drugs is rare.

The risk factors for development of psychosis in PD are the presence of dementia, sleep disturbance, advanced age, depression, past history of psychotic symptoms, night-time use of long acting dopaminomimetics and polypharmacy. The pathophysiology is unknown. Proposed mechanisms involve overstimulation of mesocorticolimbic dopamine receptors and serotonergic/dopaminergic imbalance. Dopaminomimetic agents may induce over-

stimulation of dopaminergic receptors in the frontal and limbic projection areas and result in psychotic symptoms.

Psychotic symptoms in PD are characterised by illusions, hallucinations, delusional states, paranoid ideation, altered sexual behaviour, agitation and confusion. Sleep disruption and/or vivid dreams are believed to be predictive of dopaminergic psychosis. The visual hallucinations are typically formed, non-threatening, stereotyped images of people, animals and less commonly of objects. Insight is usually preserved. Auditory, olfactory, gustatory and tactile hallucinations can occur but are not frequent. Delusions are often paranoid and jealousy is prominent. Should hallucinations occur early after the initiation of dopaminergic drugs, alternative diagnoses should be considered such as comorbid psychotic illness or non-PD parkinsonian syndromes.

Psychosis is a major risk factor for permanent nursing home placement and is associated with a high mortality

Management

Treatment of psychosis in PD can be very difficult because it may worsen motor function (Table 4). If the psychotic symptoms are relatively trivial, drug treatment may not be necessary. The first step is to identify and eliminate any external factors that may provoke or facilitate psychotic symptoms, including undue or inappropriate external stimuli. In addition, metabolic or endocrine encephalopathy, malnutrition, dehydration, drug intoxication, concomitant nervous system disease or infections should be excluded, especially if confusion is present. The second step is the withdrawal of anticholinergics, amantadine, selegiline, dopamine agonists and COMT inhibitors followed by reduction of levodopa dosage. It is best to gradually taper and discontinue one drug at a time, rather than reducing them all at once. In particular, night-time doses of medications should be withdrawn or taken earlier in the day. Levodopa holidays have serious potential complications such as the neuroleptic-malig-

Table 4 The stepwise approach to management of psychosis in Parkinson's disease

Exclude systemic and metabolic disorders, drug intoxication
Minimize evening doses of antiparkinsonian drugs
Discontinue antiparkinsonian drugs in the following order: anticholinergics, amantadine, selegiline, dopamine agonists, and COMT inhibitors – gradually
Gradually reduce levodopa dose (provided no marked and unacceptable deterioration in parkinsonism)
Add atypical neuroleptics in the following order: quetiapine, clozapine, olanzapine
Try alternative drugs (ondansetron, carbamazepine, benzodiazepines, antihistaminergics, cholinesterase inhibitors)
Electroconvulsive therapy

Levodopa holidays have serious potential complications and should be avoided

nant syndrome and should be avoided. If psychotic symptoms do not improve, or motor function worsens with reduced dopaminergic treatment, atypical neuroleptics should be tried.

Atypical neuroleptic drugs

Typical neuroleptic drugs such as haloperidol or chlorpromazine should be avoided. These drugs block dopaminergic D-2 receptors and can cause worsening of motor symptoms. Atypical neuroleptics are the drugs of choice. These agents selectively antagonize mesolimbic dopamine and serotonin receptors with relative sparing of the nigro-striatal pathways and thus are unlikely to induce extrapyramidal adverse effects. Atypical neuroleptics have affinity for dopaminergic, histaminergic, serotonergic, cholinergic and alpha-adrenergic receptors. Hence, they can induce orthostatic hypotension, drowsiness, memory impairment and confusion. Clozapine, risperidone, olanzapine, and quetiapine have been all classified as atypical neuroleptics because of their lower risk of inducing extrapyramidal adverse effects in schizophrenic patients (Friedman & Factor 2000). However, risperidone has a profile which is closer to that of typical neuroleptics, and olanzapine induces more extrapyramidal adverse effects than either clozapine or quetiapine, which should be preferred in the treatment of psychosis in PD. Atypical neuroleptics should be started at very low doses and titrated up carefully as needed.

Quetiapine

Quetiapine is a novel atypical neuroleptic with a very low potential to induce extrapyramidal symptoms. Open-label studies suggest that small doses are useful and well-tolerated in the treatment of psychosis in PD. Quetiapine has close pharmacological similarities to clozapine, but without the risk of agranulocytosis. It is probably less potent than clozapine, but better tolerated and easier to use because no blood monitoring is required. The common adverse effects include dizziness, drowsiness, nausea, lethargy, orthostatic hypotension, headache, and irritability. Amelioration of psychosis in PD is achieved with significantly lower doses than those required to treat schizophrenia. Quetiapine should be started with 12.5–25 mg at bedtime and titrated upwards

at 3–6 day intervals, up to a maximum daily dose of 450 mg, given b.d.

Clozapine

If quetiapine is not effective or not tolerated, clozapine is the second choice. Clozapine is a potent dibenzodiazepine and was the first atypical neuroleptic to be discovered. It has a low affinity for D1 and D2 receptors, a strong affinity for D4 receptors and is virtually devoid of extrapyramidal adverse effects. In multiple open-label and two double blind, placebo-controlled studies, low doses of clozapine were effective in the treatment of psychotic symptoms in patients with PD, without worsening motor function (The Parkinson Study Group 1999; The French Clozapine Parkinson Study Group 1999). Clozapine may also be useful for anxiety, depression, disturbances of sleep and appetite, hypersexuality, and akathisia. In some patients there is improvement in tremor, limb dystonia and dyskinesias (Trosch *et al.* 1998).

Mild-to-moderate granulocytopenia occurs in 1–2% and severe agranulocytosis in 0.8% of patients treated over 1 year. This reaction is idiosyncratic and is not dose-related. Agranulocytosis can be fatal, but is reversible if detected early. Weekly white blood cell counts are mandatory (at least for the first 6 months) and the drug should be immediately discontinued if granulocytopenia is detected. Agranulocytosis is more frequent in the elderly and during the first 3 months after the start of treatment. The drug is contraindicated in patients with a history of blood dyscrasia.

Other adverse effects include sedation, orthostatic hypotension, weight gain, tachycardia, seizures at high doses, confusion, hypersalivation and drooling. The dose of clozapine required to treat psychosis in patients with PD is generally much lower than in schizophrenia. The treatment should be started with very low doses such as 6.25–12.5 mg at bedtime and then gradually increased every few days until the symptoms abate or intolerable adverse effects occur. Effective doses are usually not more than 100–200 mg daily given b.d., doses up to 450–600 mg daily are rarely necessary.

Olanzapine

Should both quetiapine and clozapine fail, olanzapine is the third choice. It is another dibenzodiazepine derivative with antagonistic properties at D2 and 5HT-2 receptors. Adverse

effects include drowsiness, sedation, dizziness, dry mouth and raised liver enzymes without clinical correlate. Agranulocytosis has not been a problem. This drug is effective in treating psychotic symptoms in patients with PD, but doses higher than 5 mg may worsen motor function (Goetz *et al.* 2000). It should be started with low doses at bedtime (1.25–2.5 mg/day) and the dose increased slowly until psychosis improves or motor function worsens.

Risperidone

Risperidone is a benzisoxazole derivative with potent antagonism at 5HT-2, dopamine D2 and adrenergic receptors, but not at cholinergic receptors. At low doses (0.5–1 mg/day) it is effective in treating psychosis in patients with PD. It is, however, not an atypical neuroleptic in the strict sense and can worsen motor symptoms or induce parkinsonism in other patient populations (Meco *et al.* 1994). Long-term use should be avoided because of potentially serious extrapyramidal adverse effects – it is a last resort.

Other approaches

Ondansetron is a selective serotonin 5HT-3 receptor antagonist commonly used as an anti-emetic. In a few open-label studies, doses up to 12–24 mg/day have been reported to help psychotic symptoms in patients with PD (Zoldan *et al.* 1995). The drug is well-tolerated with no major adverse effects and it can be administered parenterally. It is, however, very expensive and not suitable for long-term treatment.

Should all else fail, carbamazepine can be tried although there have been no formal studies in the treatment of psychosis associated with PD. Benzodiazepines such as clonazepam and diazepam, or antihistaminergic drugs such as diphenhydramine, may be useful against psychotic agitation. In demented patients with PD, delusions and hallucinations might be caused by cholinergic deficits and cholinesterase-inhibitors such as rivastigmine or donepezil may be useful – such beneficial effects have been reported in patients with dementia with Lewy bodies (Shea *et al.* 1998; McKeith *et al.* 2000).

If patients fail to respond to any medical treatment and if there is no coincident dementia, ECT can be considered. This may, however, cause confusion and memory disturbances.

COGNITIVE IMPAIRMENT AND DEMENTIA

Dementia occurs eventually in up to 40% of patients with PD. It is more common in older patients and in late stage disease. In addition to overt dementia, subtle cognitive changes, especially in the executive domain, are commonly seen. Dementia in PD is usually of the dysexecutive type, with severe impairment of executive functions, attention and prominent behavioural symptoms. Memory impairment is usually due to reduced speed of storage and impaired retrieval; limbic type amnesia akin to that seen in Alzheimer's disease is less common. The mechanism of these cognitive changes is not certain, but may involve dopaminergic, noradrenergic, serotonergic and cholinergic deficits, in addition to other mechanisms such as cortical cell loss and Lewy body or Alzheimer-type pathology. Depression may sometimes contribute to cognitive impairment. Metabolic imbalance or dehydration can induce or worsen cognitive deficits as well as anticholinergic drugs, amantadine, anxiolytics and sedatives. Therefore these drugs should be avoided in the elderly and cognitively impaired patients.

Confusion is characterised by sudden onset, fluctuating alertness and cognitive function, agitation, attention deficit, and an abnormal electroencephalogram. Infections, metabolic and endocrine disturbances, malnutrition, dehydration, concomitant CNS disease and many drugs (selegiline, amantadine, anticholinergics, benzodiazepines, antidepressants) can induce confusional states. Sometimes treatment of the underlying pathology reverses confusion completely.

Dementia with Lewy bodies is thought to be the second most common form of dementia in the elderly. It is characterised by progressive cognitive decline, with significant fluctuations in alertness, psychosis with recurrent hallucinations, neuroleptic sensitivity, falls and parkinsonism (McKeith *et al.* 1996). Pathological studies reveal more prominent and severe deficits in subcortical and cortical cholinergic activity than those seen in Alzheimer's disease (Samuel *et al.* 1997).

Management

In patients who develop dementia or cognitive decline, the first step should be to withdraw any drugs that may induce cognitive impairment

(such as anticholinergics) (Table 5); and also to exclude systemic disorders as well as any concomitant diseases, particularly treatable ones. Dementia in patients with PD does not respond to dopaminergic treatment. Cholinesterase inhibitors have been reported to improve cognition and psychosis to some extent in PD patients with dementia and should be considered (Hutchinson & Fazzini 1996). New generation cholinesterase inhibitors such as rivastigmine and donepezil are safe and relatively well-tolerated if titrated slowly. They do not seem to worsen motor symptoms. Common adverse effects include those related to the gastrointestinal system such as nausea, vomiting, loss of appetite, diarrhoea and sweating; headache and muscle cramps are less common.

Table 5 The management of confusion and dementia

Withdraw likely culprit drugs (e.g. anticholinergics)
 Check for systemic disturbances (electrolyte imbalance) or other disorders
 (e.g. hypothyroidism)
 Consider cholinesterase inhibitors – rivastigmine, donepezil

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