

Parkinson's disease and anxiety

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Abstract

There has been a recent surge of interest in the subject of anxiety in patients with Parkinson's disease. Up to 40% of patients with Parkinson's disease experience clinically significant anxiety. This anxiety may be a psychological reaction to the stress of the illness or may be related to the neurochemical changes of the disease itself. Antiparkinsonian drugs may have a role in the pathogenesis of the anxiety. The anxiety disorders in Parkinson's disease patients appear to be clustered in the panic disorder, phobic disorder, and generalised anxiety disorder areas. The degree of comorbidity between anxiety and depression in patients with Parkinson's disease is in excess of that found in patients without the disease and anxiety in combination with depression may represent a specific depressive subtype in Parkinson's disease. As yet, there is no trial evidence as to the treatment of anxiety in patients with Parkinson's disease.

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Although psychiatric disorders occur frequently in patients with Parkinson's disease, little attention has been given until recently to anxiety disorders in these patients. Up to 40% of patients with Parkinson's disease suffer from clinically significant anxiety: this is higher than expected for this age group of patients.¹ Anxiety may cause a significant deterioration of parkinsonian symptoms² and anxiety in association with depression may delineate a specific depressive subtype in Parkinson's disease. Anxiety may go unnoticed unless expressly sought and can have a marked effect on motivation and rehabilitation.

Prevalence

There is a wide range in the reporting of the prevalence of anxiety in patients with Parkinson's disease. Anxiety is significantly more prevalent in Parkinson's disease sufferers compared with age and sex matched non-sufferers. Menza *et al* studied 104 patients with Parkinson's disease and 61 medical control subjects with similar disability for symptoms of anxiety and depression.³ All patients completed the Zung self rating depression scale and the Zung self rating anxiety scale: the mean anxiety scale was 25.2 in patients with Parkinson's disease and 20.9 in control patients. Thus patients scored significantly higher than control subjects did on this measure of anxiety ($p < 0.001$).

Gotham *et al* assessed patients with Parkinson's disease, patients with arthritis, and

normal controls with the Beck depression inventory, the Beck hopelessness scale, and the Spielberger anxiety index.⁴ The patients with Parkinson's disease scored significantly higher than the normal controls on these assessment scales but did not differ from those with arthritis. The prevalence of anxiety disorders in patients with Parkinson's disease ranges from 5.3% to 40%.^{5,6} Stein *et al* systematically evaluated 24 patients with idiopathic Parkinson's disease for the presence of Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R axis I syndromes.⁷ They found that nine of 24 parkinsonian patients had clinically important anxiety disorder: severity of anxiety was not correlated with severity of parkinsonian symptoms, duration of levodopa use, or current dose of levodopa. Starkstein *et al* found that 40% of patients with Parkinson's disease met DSM-III criteria for generalised anxiety disorders.⁶ While anxiety was significantly associated with depression, some patients showed anxiety without depression. Anxiety was not associated with greater physical or cognitive impairment in this study. Menza *et al* evaluated 42 patients with Parkinson's disease and 21 matched medical controls using DSM-III-R criteria, the Zung depression questionnaire, and the Zung self administered anxiety questionnaire.⁸ Twelve patients with the disease but only one medical control had a formal anxiety disorder diagnosis. Of the 12 Parkinson's disease patients with an anxiety disorder diagnosis, 11 had a comorbid depressive disorder diagnosis.

Research has shown that the prevalence of panic attacks plus depression in Parkinson's disease is higher than in the general population. Hillen and Sage asked 130 patients with Parkinson's disease and motor fluctuations about symptoms they experienced in the "off" state: four patients described symptoms of panic.⁹ Vasquez *et al* found that 31 out of 131 levodopa treated patients suffered from panic attacks.¹⁰ They found a clear cut relationship of panic disorder with the presence of depression, motor fluctuations, and treatment with higher doses of levodopa. Lauterbach and Duvoisin investigated the lifetime prevalence of DSM-III defined anxiety disorders in Parkinson's disease patients; they found the lifetime prevalence of panic disorder to be 7.9%.⁵ Rubin *et al* used DSM-III-R criteria for anxiety disorders to evaluate 16 Parkinson's disease patients (from a total population of 210 patients) who reported marked episodic anxiety; eight patients met criteria for panic anxiety disorder and six of these also met criteria for major depression or dysthymia.¹¹

In contrast, most studies of subjects without the disease showed that anxiety disorders are less common in elderly people than in younger

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adults. The Epidemiologic Catchment Area study investigated the prevalence of anxiety disorders in 18 571 adults in America (5702 were 65 years or older).¹² The investigators found the overall prevalence of anxiety disorders to be 5.5% in people over the age of 65 years (compared with 7.3% in subjects of all ages); the prevalence of phobic disorder, panic disorder, and obsessive-compulsive disorder was also lower in patients over the age of 65 years. Bland *et al* surveyed the six month prevalence rates of anxiety disorders in 3258 people (358 were 65 years or older).¹³ The prevalence rates for all anxiety disorders was 3.5% in people aged ≥ 65 years living independently, 5.5% in people aged ≥ 65 years living in institutions, and 6.5% in subjects of all ages.

Pathophysiology

It is not known why there is an increased prevalence of anxiety disorders in patients with Parkinson's disease.

Anxiety may be a psychological response to the physical symptoms. Patients with Parkinson's disease experience considerably higher stress than people without the disease.¹⁴ Patients with Parkinson's disease may suffer from social anxiety: patients are afraid of being negatively evaluated in public. Anxiety and social withdrawal may then result. However, Schiffer *et al* found a much higher frequency of generalised anxiety disorders and panic attacks in depressed parkinsonian patients than in depressed multiple sclerosis patients.¹⁵

The anxiety in patients with Parkinson's disease may be related to the neurochemical changes of the disease itself. Norepinephrine, serotonin, dopamine, and γ -aminobutyric acid (GABA) have been implicated in the pathogenesis of anxiety.¹⁶⁻¹⁹ Abnormalities of these neurotransmitter systems have been shown in patients with Parkinson's disease²⁰; however, these abnormalities have not been proved to be linked to the pathogenesis of anxiety in this disorder.

Anxiety in Parkinson's disease patients could involve a dopaminergic deficit directly⁷ or could be due to interactions between dopaminergic deficits and the variable deficits in norepinephrine and serotonin that are known to occur in Parkinson's disease.^{5 21} Both the ventral tegmental area and the locus ceruleus (which give rise to mesolimbic and noradrenergic pathways respectively) show significant neuronal loss in Parkinson's disease. Dopamine inhibits the rate of firing of the locus ceruleus and the loss of dopaminergic inhibition could explain the high prevalence of anxiety disorders in patients with the disease.²¹

Anxiety may be caused by abnormalities in the action of serotonin. A functional polymorphism in the promoter region of the serotonin transporter gene has recently been linked to anxiety. Menza *et al* found that patients with Parkinson's disease who carried the short allele of the serotonin transporter scored significantly higher than non-carriers on anxiety scales.²² This suggests that genetic defects may play a part in the pathogenesis of anxiety in Parkinson's disease.

Berlan *et al* suggested that untreated Parkinson's disease is associated with a significant decrease in α_2 -adrenergic sensitivity.²³ Patients with Parkinson's disease may be more susceptible to panic attacks because they have an alteration of α_2 -adrenergic receptors.

Lauterbach and Duvoisin found that anxiety disorders and classical panic disorder typically precede the onset of familial parkinsonism,⁵ whereas atypical panic phenomena start after familial parkinsonism onset. These phenomena suggest that early dopaminergic pathway degeneration may disinhibit the locus ceruleus and cause anxiety symptoms before the onset of parkinsonian signs.

Hollander *et al* found impairment on visuo-constructional tasks but not on tasks of immediate memory and focused attention in patients with obsessive-compulsive disorder and in patients with Parkinson's disease²⁴; this may suggest common selective deficits in these two disorders. "Autonomic" symptoms are more frequent in patients with Parkinson's disease than in the general population. Berrios *et al* found that autonomic symptoms in such patients are significantly associated with depression and anxiety.²⁵ Kurlan *et al* administered yohimbine (an α_2 -antagonist) to six anxious Parkinson's disease patients: three patients developed a panic attack.²⁶ Richard *et al* performed an oral yohimbine challenge in six patients with Parkinson's disease and anxiety: these patients developed panic attacks at frequencies comparable to patients with primary panic disorder.²⁷

Anxiety and laterality of Parkinson's disease

A number of studies have examined the relationship between anxiety and laterality of parkinsonian symptoms. These studies have shown that anxiety in patients with Parkinson's disease was associated with mainly left sided symptoms.^{11 28} If anxiety in patients with Parkinson's disease was a psychological response to disability, then patients with right sided parkinsonism (affecting their dominant hand) would be expected to be more anxious: in fact the opposite is the case.

Anxiety and antiparkinsonian medications

There is no consensus on whether antiparkinsonian medications are responsible for symptoms of anxiety in Parkinson's disease.

Stein *et al* found that the levodopa dose was similar in anxious and non-anxious patients.⁷ Henderson *et al* noted that 44% of patients with Parkinson's disease noticed anxiety symptoms before starting levodopa.²⁹ Menza *et al* found that the levodopa dose did not significantly correlate with anxiety levels: they suggested that anxiety in patients with Parkinson's disease is unlikely to be a side effect of levodopa treatment.⁸ In contrast, Vasquez *et al* found that panic attacks were related to levodopa therapy but not to other agonist drugs.¹⁰

Lang reported anxiety in five of 26 patients when pergolide was added to their treatment

Box 1: Anxiety disorders found in Parkinson's disease

- Generalised anxiety disorder
- Panic disorder
- Social phobia
- Phobic disorder
- Agoraphobia
- Obsessive-compulsive disorder
- Anxiety disorder not otherwise specified

regimen.³⁰ Menza *et al* found no differences in measures of anxiety in patients receiving or not receiving pergolide.⁸ Menza *et al* found no differences in measures of anxiety in patients receiving or not receiving selegiline.⁸

The temporal relationship between panic attacks and off periods have led some authors to suggest that panic attacks may be related to falling brain levodopa levels.¹⁵ Anxiety fluctuations may be an important component of levodopa induced fluctuations.³¹ In a double blind placebo controlled trial, Maricle *et al* found that anxiety levels fell and motor performance improved during a levodopa infusion.³²

Types of anxiety disorders found in parkinson's disease

Generalised anxiety disorder, panic disorder, social phobia, phobic disorder, agoraphobia, obsessive-compulsive disorder, and anxiety disorder not otherwise specified have all been identified in patients with Parkinson's disease (box 1).^{5 7 8} The diagnoses in the patients with Parkinson's disease appear to be clustered in the panic disorder, phobic disorder, and generalised anxiety disorder areas.^{5 7 8 15}

Anxiety and depression

Anxiety and depression commonly coexist in the same patient.³³ However, there appears to be a special relationship between anxiety and depression in Parkinson's disease. Patients with the disease have significantly higher levels of depression and anxiety than normal controls.⁴ Henderson *et al* found that depression in combination with panic and/or anxiety occurred in 38% of parkinsonian patients compared with 8% of healthy spouse controls: depression and anxiety were highly correlated in patients with Parkinson's disease.²⁹ Twenty per cent of these patients reported the onset of depression and/or anxiety before the onset of physical symptoms. Menza *et al* found that 92% of patients with Parkinson's disease who had an anxiety disorder diagnosis also had depressive disorders or symptoms and 67% of patients with a depressive disorder had an anxiety disorder diagnosis.⁸ Copeland *et al* found that the degree of comorbidity between anxiety and depression in patients with Parkinson's disease is in excess of that found in those without.³³

Dementia, anxiety, and Parkinson's disease

The relationship between dementia and anxiety in patients with Parkinson's disease is uncertain. A number of studies have found no relationship between dementia and anxiety in

those with the disease.^{28 34} Stein *et al* has postulated that abnormal dopaminergic regulation may be the cause of anxiety in Parkinson's disease patients and that the high prevalence of anxiety may be only for non-demented patients.⁷ Norepinephrine has been hypothesised to cause anxiety and there is a significant decrease in brain levels of norepinephrine in demented Parkinson's disease patients.³⁵

Iruela *et al* also speculated that the prevalence of anxiety is lower in demented than in non-demented patients²¹; a study by Lauterbach failed to confirm this.³⁴

Anxiety and motor performance

A number of studies have found that the severity of Parkinson's disease is not related to anxiety.^{7 8}

The relationship between anxiety and motor fluctuations is fascinating. Significant changes in anxiety levels may accompany the "on-off" symptoms in patients with fluctuating Parkinson's disease.^{8 29 36} However, a number of studies have not found this phenomenon.^{5 7 37} A number of studies have examined anxiety in patients Parkinson's disease with on-off symptoms; these have found that patients have more anxiety in the off state than in the on state.^{7 10 29 36-38} In a study of 19 patients with idiopathic Parkinson's disease, Siemers *et al* found that the magnitude of the increase in anxiety level during off periods was correlated with the change in parkinsonian symptoms.³⁸ Menza *et al* found that anxiety levels also increased when patients suffered from dyskinesias.³⁶

However, Lauterbach and Duvoisin noted the attenuation of panic attacks in patients with familial Parkinson's disease with the advancement of disease and the onset of parkinsonian freezing.⁵ Kurlan *et al* found that, even during yohimbine induced panic attacks, patients suffered no worsening of their parkinsonian symptoms.²⁶ It is not known whether anxiety and decreased mobility are due to common neurobiological mechanisms or if the anxiety is a reaction to the physical symptoms.

Sleep, anxiety, and Parkinson's disease

Patients with Parkinson's disease often suffer from poor sleep onset, poor sleep maintenance, and nightmares.

Menza and Rosen examined the effect of anxiety on sleep in Parkinson's disease; they found that patients with the disease had poorer overall sleep quality, longer sleep latency, and more night time awakenings than controls.³⁹ They found that anxiety was significantly correlated with feeling unrefreshed in the morning; despite this, anxiety did not contribute significantly to the overall variance of sleep quality, which was dominated by the effect of Parkinson's disease itself.

Anxiety and the Parkinson plus syndromes

Fetoni *et al* found higher levels of anxiety in patients with idiopathic Parkinson's disease than in patients with multisystem atrophy.⁴⁰ After levodopa, anxiety in patients with idio-

pathic disease improved significantly whereas the affective symptoms in patients with multi-system atrophy did not change.

Litvan *et al* found that patients with corticobasal degeneration commonly exhibited depression (73%), apathy (40%), irritability (20%), and agitation (20%) but less often had anxiety.⁴¹

Management

There is no trial evidence as to the treatment of anxiety in patients with Parkinson's disease.

In patients who appear to be anxious as a result of medication, dose reduction or substitution of a different medication may be the best approach. In patients who experience attacks of anxiety during off periods, therapy should be directed at reducing off time by adjusting anti-Parkinson's disease medications.⁴²

Elderly patients are more sensitive to benzodiazepines due to their tendency towards falls and over-sedation and concomitant medical conditions. The majority of patients with Parkinson's disease are elderly so these agents should be used with caution. Long half life benzodiazepines should be avoided in older patients. Benzodiazepines should be used for short periods only. There is evidence that benzodiazepines may increase parkinsonian symptoms.⁴³

Low dose tricyclic antidepressants with low anticholinergic effects may be useful in those patients who do not respond to benzodiazepines.⁴⁴

Buspirone may be used in the short term treatment of anxiety. Bonifati *et al* found that buspirone significantly lessened the severity of levodopa induced dyskinesias in patients with Parkinson's disease; however, there were no changes in the mild anxiety symptoms during the study.⁴⁵ Ludwig *et al* found that buspirone was well tolerated by parkinsonian patients at conventional antianxiety doses of 10–40 mg/day; at higher doses (100 mg/day), buspirone increased parkinsonian symptoms.⁴⁶

If a patient is suffering from anxiety and depression, a selective serotonin reuptake inhibitor may be effective. However, there is controversy about the role of these drugs in Parkinson's disease. Jansen Steur reported increased motor disability in four patients with idiopathic Parkinson's disease after exposure to fluoxetine.⁴⁷ Parkinsonism exacerbated by paroxetine has also been reported.⁴⁸ In a retrospective review of patients with Parkinson's disease, Caley and Friedman found that fluoxetine in doses up to 40 mg/day does not appear to be associated with exacerbations of parkinsonian symptoms.⁴⁹ Montastruc *et al*, in a prospective open trial, did not find any significant increase in parkinsonian symptoms after treatment with fluoxetine for one month: they hypothesised that fluoxetine induced parkinsonism could be due to individual susceptibility.⁵⁰

Neuroleptic medication causes significant extrapyramidal side effects and are not appropriate for the treatment of anxiety in patients with Parkinson's disease. β -Blockers have been used to lessen tremor in Parkinson's disease and may have a small antianxiety effect.

Psychological interventions often help patients with secondary psychological symptoms of Parkinson's disease. The goal of such interventions is to help the patient cope with stressful social situations. The strategies include relaxation and cognitive restructuring, together with situational behavioural analysis and training in social skills specifically adapted to the disease. Patients should be given time to discuss their physical, psychological, and social problems; therapists should provide practical help, and social assistance should be proffered when necessary. However, there is no evidence of significant enduring effects of psychological interventions on the physical symptoms of Parkinson's disease.

Future

We do not know the duration of anxiety in patients with Parkinson's disease; only longitu-

Questions (answers at end of paper)

Q1. The following neurotransmitters have been implicated in the pathogenesis of anxiety:

- (A) Norepinephrine
- (B) Serotonin
- (C) Dopamine
- (D) γ -Aminobutyric acid (GABA)

Q2. Patients with Parkinson's disease have an increased prevalence of the following psychiatric disorders:

- (A) Phobic disorder
- (B) Depression
- (C) Generalised anxiety disorder
- (D) Panic disorder
- (E) Schizophrenia

Q3. The following statements are true of benzodiazepines:

- (A) Elderly patients are less sensitive to benzodiazepines than young patients
- (B) Long half life benzodiazepines should be avoided in older patients
- (C) Benzodiazepines should be used only for short term treatment of insomnia
- (D) Benzodiazepines may increase parkinsonian symptoms in patients with Parkinson's disease
- (E) Shorter acting benzodiazepines carry a greater risk of withdrawal reactions

Q4. The following statements are true:

- (A) Up to 40% of patients with Parkinson's disease suffer from clinically significant anxiety
- (B) Anxiety and depression rarely occur together in patients with Parkinson's disease
- (C) Patients with Parkinson's disease and motor fluctuations usually suffer from more anxiety in the "on" state than in the "off" state
- (D) Many patients with Parkinson's disease have poor sleep quality
- (E) Buspirone may be used in the short term treatment of anxiety

Learning points

- Up to 40% of patients with Parkinson's disease experience clinically significant anxiety
- The anxiety in Parkinson's disease patients may be related to the neurochemical changes of the disease itself
- The anxiety disorders in Parkinson's disease patients appear to be clustered in the panic disorder, phobic disorder, and generalised anxiety disorder areas
- The degree of comorbidity between anxiety and depression in Parkinson's disease patients is in excess of that found in patients without Parkinson's disease
- There is no trial evidence as to the treatment of anxiety in patients with Parkinson's disease

dinal studies will demonstrate the importance of anxiety as a pervasive psychiatric problem. Further studies are needed to elucidate the complex neurobiological causes of anxiety in these patients. Investigators must explore the links between anxiety, depression, and dementia in patients with Parkinson's disease. Controlled trials will be needed to discover what is the best way to treat these anxiety disorders.

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Answers: true (T)/false (F)

- (A) T, (B) T, (C) T, (D) T; 2. (A) T, (B) T, (C) T, (D) T, (E) F; 3. (A) F, (B) T, (C) T, (D) T, (E) T; 4. (A) T, (B) F, (C) F, (D) T, (E) T.



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