Anxiety in Parkinson's disease: identification and management

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Abstract: Anxiety disturbances are recognized as common psychiatric comorbidities in Parkinson's disease (PD) and contribute to significant impairments in areas of cognitive, functional, motor and social performance. Anxiety in PD results in reduced quality of life, higher levels of care dependency and increased caregiver burden. Surprisingly, there is a paucity of treatment data. In one randomized, controlled study, bromazepam was found to be effective for anxiety in PD. However, usage of benzodiazepines in the PD population is limited by potential risk of confusion and falls. There are no controlled studies of selective serotonin reuptake inhibitors (SSRIs) for anxiety in PD. However, results from uncontrolled studies suggest that SSRIs are effective for anxiety in PD, although in these studies anxiety outcomes were secondary. This review underscores that, given the high prevalence of anxiety disturbances in PD, there is a significant paucity of treatment data for this population. Additional studies are warranted. In the meantime, clinicians should rely on empiric assessments of known risks and putative benefits to guide treatment decisions. Cognitive and behavioral therapies (with or without pharmacotherapy) have demonstrated efficacy and warrant consideration. When feasible, a targeted and individualized multimodal approach utilizing psychotherapeutic interventions along with pharmacologic therapies should be considered.

Keywords: Anxiety, neurology, Parkinson's disease, psychiatry

Introduction

Anxiety disturbances are recognized as common nonmotor, psychiatric comorbidities in idiopathic Parkinson's disease (PD) that contribute to reductions in quality of life, higher levels of care dependency and increased caregiver distress [Hanna and Cronin-Golomb, 2012; Riedel *et al.* 2012; Pontone *et al.* 2011; Weintraub *et al.* 2004; Mathias, 2003; Global Parkinson's Disease Survey Steering Committee, 2002; Cubo *et al.* 2000; Richard *et al.* 1996]. However, anxiety disturbances appear to be under-recognized and undertreated in patients with PD due to diagnostic imprecision, symptom overlap with motor and cognitive features of PD, complexity of diagnosis, healthcare access and resources, and under-reporting of symptoms by patients and caregivers [Gallagher *et al.* 2010; Marsh *et al.* 2006; Weintraub *et al.* 2003]. This review summarizes the most recent data on epidemiology, possible mechanisms, and recognition of anxiety

in PD and identifies a significant paucity of treatment data.

Epidemiology

In James Parkinson's original monograph, *An Essay on the Shaking Palsy*, brief mention was made of the nonmotor symptoms of anxiety [Ostheimer, 1922]. However, it is now known that clinically significant anxiety symptoms occur in between 20% to greater than 50% of PD patients, a frequency greater than that found in community dwelling age-matched controls [Pontone *et al.* 2011; Richard *et al.* 1996; Dissanayaka *et al.* 2010; Shulman *et al.* 2002]. Notably, anxiety and depressive syndromes frequently co-occur. Menza and colleagues reported a depressive disorder in 92% of PD patients diagnosed with an anxiety disorder, and an anxiety disorder was present in 67% of depressed PD patients [Menza *et al.* 1993]. This is consistent

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with results by Starkstein and colleagues reporting co-occurrence of depression in 76% of patients with PD and anxiety [Starkstein *et al.* 1993].

In addition to generalized anxiety disorder (GAD), patients with PD, regardless of gender, also experience panic disorders and social phobias with a prevalence of approximately 30% [Stein *et al.* 1990; Nuti *et al.* 2004; Vazquez *et al.* 1993]. Some patients with PD may perceive themselves as 'disfigured' and may experience significant distress in social interactions and develop social anxiety in the context of PD [Bolluk *et al.* 2010]. Anxiety contributes to mental and somatic discomfort as well as to existing motor symptoms or fluctuations. For example, patients will report that episodic states of anxiety aggravate preexisting tremor or dyskinesia, and fear of falling has been associated with impaired postural stability. In patients with PD, the presence of anxiety often co-exists with somatic preoccupation or somatization, although the correlation has not been studied *per se* [Siri *et al.* 2010]. Patients with anxiety and high levels of somatization tend to utilize medical care more frequently [Tomenson *et al.* 2012]. Anecdotally, we have observed this in patients with PD. Consequently, in patients with high levels of anxiety or significant episodic anxiety, initiation of appropriate anxiolytic therapy may improve motor symptoms as well as mental and psychosocial functioning, and perhaps reduce health care utilization.

Mechanisms

Several theories have been proposed to explain the occurrence of anxiety in PD, but overall, little is known. Anxiety in PD is attributed to a combination of medical, neurochemical and psychosocial phenomena. In a subset of patients, anxiety disorders are a 'reactive' response secondary to the diagnosis of PD. However, when compared with non-PD patients with chronic illnesses and similar disability, anxiety in patients with PD is significantly more severe [Schiffer *et al.* 1988]. Epidemiologic observations indicate that patients with PD are at greater risk of developing anxiety disorders before the diagnosis of PD [Weisskopf *et al.* 2003; Shiba *et al.* 2000]. These findings suggest that anxiety may be an early nonmotor phenotype of PD and that disability, although it may contribute to anxiety, is not the sole etiologic determinant.

Episodic anxiety has been associated with motor fluctuations [Racette *et al.* 2002; Witjas *et al.* 2002; Friedenberg and Cumming, 1989]. During 'off' phases, patients may experience feelings of despair, hopelessness and panic that dissipate during the 'on' phases [Vazquez *et al.* 1993]. Frequency of freezing is also highly correlated with the presence of panic disorders and secondary panic attacks [Lauterbach *et al.* 2003]. However, emotional fluctuations do not always correlate temporally with motor state [Richard *et al.* 2004; Nissenbaum *et al.* 1987]. In a study of 87 patients with PD, 29% had fluctuations in anxiety, 24% in motor and 21% in mood [Richard *et al.* 2004]. Of the patients with motor fluctuations, 75% had mood or anxiety fluctuations that did not necessarily correlate with motor state. Although the pattern of anxiety or mood fluctuations can be heterogeneous, adjustment of antiparkinsonian medications to minimize the motor fluctuations can be beneficial.

Neurochemically, degeneration of subcortical nuclei and ascending dopamine, norepinephrine and serotonin (5-HT) pathways within the basal ganglia-frontal circuits may be responsible for symptoms of anxiety [Prediger *et al.* 2012; Kano *et al.* 2011; Kerenyi *et al.* 2003; Remy *et al.* 2005]. Remy and colleagues utilized [¹¹C]RTI-32 positron emission tomography (PET), an *in vivo* marker of both dopamine and norepinephrine transporter binding, to localize differences between eight depressed and 12 nondepressed patients with PD matched for age, disease duration and antiparkinsonian medication [Remy *et al.* 2005]. Exploratory analyses revealed that the severity of anxiety in the PD patients was inversely correlated with binding of [¹¹C]RTI-32 in the amygdala, locus coeruleus and thalamus. These results suggest that anxiety in PD might be associated with a specific loss of dopaminergic and noradrenergic innervation in the locus coeruleus and the limbic system.

Detection and assessment

An attentive and careful history is vital for recognition of anxiety disturbances in the patient with PD. Specific inquiry about symptoms should occur, especially when the history provided by the patient or family suggests that anxiety phenomena are prominent in the context of day-to-day function or in relationship to medication effects, as with 'on-off' fluctuations. While the fundamental feature of an anxiety disorder consists of unwarranted apprehension or anxiety, establishing the diagnosis of an

anxiety disorder can be challenging in patients with PD. Diagnostic imprecision may occur because several symptoms of anxiety overlap with mental and somatic symptoms commonly associated with PD, anxiety symptoms may be attributed to agitated depression, psychotic anxiety, or a mixed state within the affective spectrum. In addition, many patients have clinically significant anxiety that does not correspond directly to *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition* (DSM-IV) criteria [American Psychiatric Association, 2000]. For example, GAD in the general population includes a period of at least 6 months with prominent tension, worry and feelings of apprehension about everyday events and problems, along with the presence of at least three of six other symptoms, including sleep disturbance, difficulty concentrating, muscle tension and three others. Panic attacks require unprovoked episodes of severe apprehension accompanied by at least four of 22 various autonomic, psychic and somatic symptoms [American Psychiatric Association, 2000]. However, since several of the accompanying symptoms, such as tremor, concentration difficulties, dizziness, muscle aches, and numbness or tingling, are also commonly attributed to PD, they may not be recognized as components of an anxiety disorder. Of note, patients with anxiety may report an uncomfortable sensation of internal tremor (i.e. feeling of tremor within the chest, abdomen, arms or legs that cannot be seen) that may or may not be relieved by antiparkinsonian medications [Shulman *et al.* 1996a].

Given that anxiety appears to be common over the course of PD, periodic assessment would significantly enhance detection. In a clinic-based study, Shulman and colleagues reported that recognition of anxiety more than doubled (from 19% to 39%) when patients were screened with the Beck Anxiety Inventory (BAI) [Shulman *et al.* 2002]. The BAI, the Hamilton Anxiety Rating Scale and the Hospital Anxiety and Depression Scale – anxiety subscale (HADS-A) have been examined clinimetrically, but demonstrate variable performance as predictors of anxiety disorders in the PD population [Leentjens *et al.* 2011]. This may be a function of the heterogeneity of anxiety disturbances in general as well as the presence of PD-specific anxiety disturbances, e.g. on–off fluctuations with associated anxiety.

As such, efforts are underway to develop a scale that will be useful in PD patients as a screening tool and also to assess anxiety severity [Leentjens

et al. 2011; Rodriguez-Blazquez *et al.* 2009; Forjaz *et al.* 2009; Mondolo *et al.* 2007; Beck *et al.* 1998; Zigmond and Smith, 1983; Marinus *et al.* 2002; Matheson *et al.* 2012]. Because anxiety and depressive symptoms are frequently comorbid in PD, a finding of anxiety should also prompt a screening for depression. However, routinely administered, standalone screening or case-finding instruments for anxiety have limited or no benefit in the absence of enhanced patient care and clinician support (e.g. structured care involving nonmedical specialists, such as case managers, along with mental health clinicians to augment primary care) [Gilbody *et al.* 2001]. Therefore, coordination of follow up and availability of mental health services are necessary components for improving outcomes related to treatment of anxiety.

Treatment

Agents that possess anxiolytic properties include benzodiazepines, beta-blockers, buspirone, diphenhydramine, gabapentin, hydroxyzine, lamotrigine, mirtazapine, nefazodone, pregabalin, quetiapine, SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), trazodone, tricyclic antidepressants (TCAs) and vilazodone. Of these, benzodiazepines, buspirone and SSRIs have been evaluated for the treatment of anxiety in PD (*vide infra*) [Casacchia *et al.* 1975; Ludwig *et al.* 1996; Menza *et al.* 2004; Tarczy and Szombathelyi, 1998; Shulman *et al.* 1996b]. However, the primary objective of most of these studies was the assessment of depression; with anxiety as a secondary outcome. Thus, the studies were not designed or powered with anxiety as a primary outcome and although all patients were depressed, not all were anxious.

Nonpharmacological therapies, including cognitive and behavioral therapies (with or without pharmacotherapy) have also been evaluated and found effective [Dobkin *et al.* 2011; Yang *et al.* 2012; Armento *et al.* 2012]. For patients with severe, medication-resistant anxiety or when the anxiety disorder is life threatening (e.g. because of suicidality or inanition), serial electroconvulsive therapy should be considered [Marino and Friedman, 2013; Moellentine *et al.* 1998].

Benzodiazepines

Although benzodiazepines are commonly used in the management of anxiety, only one randomized controlled trial has addressed this in the PD population [Casacchia *et al.* 1975]. Bromazepam, a

long-acting benzodiazepine, was reported to improve psychic and somatic (i.e. tremor) symptoms of anxiety [Casacchia *et al.* 1975]. Anecdotally, other benzodiazepines are also been noted to be effective. In a case report, clonazepam was reported to be effective in a patient with anxiety and panic attacks that were refractory to alprazolam, lorazepam and numerous antidepressants [Chuang and Fahn, 2001]. Although benzodiazepines may be effective, their long-term use, especially in elderly or frail patients, is associated with unfavorable effects on alertness, cognition and gait, and an increased risk of falls [Cumming and Le Couteur, 2003]. However, benzodiazepines may be useful for patient with anxiety and comorbid sleep disorders such as insomnia or rapid eye movement sleep behavior disorder. Overall, benzodiazepines should be used judiciously with careful evaluation of known risks and putative benefits.

SSRIs

The SSRIs and SNRIs have not been studied *per se* for anxiety syndromes in PD in a randomized, controlled manner. In a recent 12-week, randomized, double-blinded, placebo-controlled study ($n = 115$) for the SAD-PD Study Group, there were no significant differences in treatment effect between placebo, paroxetine and venlafaxine extended-release on the secondary outcome of anxiety [Richard *et al.* 2012]. Given that paroxetine and venlafaxine possess anxiolytic properties, this finding is surprising. However, the results should be interpreted with caution as the primary intent of the study was to assess depression outcomes.

The data from uncontrolled studies suggest the SSRIs are effective for anxiety in PD [Menza *et al.* 2004; Tarczy and Szombathelyi, 1998; Shulman *et al.* 1996b]. In an open-label study ($n = 10$), Menza and colleagues reported that citalopram (mean dose 19 mg/day) improved anxiety (a secondary outcome) in depressed PD patients [Menza *et al.* 2004]. In a study of 30 depressed PD patients, paroxetine (20 mg twice daily) reduced psychic and somatic anxiety symptoms (secondary outcomes) [Tarczy and Szombathelyi, 1998]. Sertraline was also noted to have anxiolytic effects in PD patients [Shulman *et al.* 1996b]. Again, the limitation of these studies is that anxiety was a secondary outcome.

The SSRIs are relatively well tolerated, although acute, treatment-emergent side effects such as agitation, akathisia, diarrhea/loose stools, insomnia,

nausea and somnolence may occur. Occasionally, SSRIs may worsen tremor, and chronic use is associated with an increased risk of developing endocrinologic and metabolic adverse effects such as hyponatremia, sexual dysfunction and weight gain [Wolters Kluwer Health, 2012]. Reversible SSRI-induced worsening of parkinsonism has also been reported but is uncommon [Gony *et al.* 2003; van de Vijver *et al.* 2002; Dell'Agnello *et al.* 2001]. For patients on concomitant monoamine oxidase-B (MAO-B) inhibitors (e.g. rasagiline, selegiline) and SSRIs, there is a theoretical concern for occurrence of 5-HT syndrome. In one survey-based study, the frequency of 5-HT syndrome in patients on concomitant selegiline was 0.24%, with 0.04% of patients experiencing serious symptoms [Richard *et al.* 1997]. In a review of several studies that assessed the combination of rasagiline with antidepressant therapy in PD, the combination was well tolerated and no 5-HT syndrome was detected [Chen, 2011]. Abrupt discontinuation of SSRIs after extended treatment may precipitate a withdrawal or discontinuation syndrome, characterized by somatic and psychological symptoms that resemble anxiety [Black *et al.* 2000]. Therefore, if discontinuation is required, a gradual tapering of the dosage is recommended, particularly with short half-life agents such as paroxetine.

Overall, due to the absence of robust empirically derived efficacy data, SNRIs and SSRIs should be used with thoughtful evaluation of known risks against putative benefits.

Miscellaneous agents

Buspirone, an anxiolytic with partial 5-HT agonism and low sedative potential has not been evaluated specifically in a controlled manner for the management of anxiety in PD. However, in a 12-week randomized, controlled study ($n = 16$) evaluating the effect of buspirone on PD motor symptoms, moderate doses (10–40 mg/day) of buspirone were associated with a modest beneficial effect on the secondary outcome of anxiety [Ludwig *et al.* 1986]. Of note, higher daily doses (i.e. 100 mg) of buspirone significantly enhanced anxiety and worsened parkinsonism.

Non-pharmacological

Cognitive behavior therapy (CBT) is based on the construct that individuals with anxiety hold distorted cognitions. The aim of CBT is to provide a structured approach to help individuals identify

maladaptive thoughts contributing to emotional discomfort and to replace them with more enabling alternatives. Evidence suggests that CBT improves anxiety symptoms in patients with PD [Armento *et al.* 2011; Dobkin *et al.* 2011; Yang *et al.* 2012]. The largest of these studies was a 10-week, randomized, controlled study ($n = 80$) that found in-person CBT was associated with greater improvement than the control group of clinical monitoring with no new intervention [Dobkin *et al.* 2011]. These treatments focus on development of self-management skills by patients and caregivers to reduce symptoms and improve function; more systematic research is needed to measure its effects and determine how best to implement the CBT therapy in patients with PD.

And finally, for patients with severe, medication-resistant anxiety or when the anxiety disorder is life threatening (e.g. because of suicidality or inanition), serial electroconvulsive therapy should be considered [Marino and Friedman, 2013; Moellentine *et al.* 1998].

Conclusion

Anxiety disturbances are prevalent nonmotor features in patients with PD. These disturbances can contribute to morbidity in patients with PD and are correlated with poor quality of life and increased caregiver burden. Various instruments may be utilized to facilitate screening, diagnosis and assessment of anxiety in PD. However, despite attempts to improve the sensitivity and specificity of these instruments for use in the PD population, uncertainties remain. The best approach may be to remain vigilant for the presence of anxiety disturbances, to have a low threshold for intervention, and to utilize an individualized approach. Patients should have access to a system of coordinated care consisting of regular follow up and involvement of mental health clinicians. Given that anxiety disturbances are common in PD, it is surprising that the data on the efficacy of treatments in this population are sparse and of small sample size. Additional treatment studies are clearly warranted. Owing to the absence of robust empirically derived efficacy data, pharmacologic agents should be used with careful evaluation of known risks against putative benefits.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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