Review

Anxiety in Parkinson's disease: A critical review of experimental and clinical studies

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting about 1% of the population older than 60 years. Classically, PD is considered as a movement disorder, and its diagnosis is based on the presence of a set of cardinal motor signs that are the consequence of a pronounced death of dopaminergic neurons in the substantia nigra pars compacta. There is now considerable evidence showing that the neurodegenerative processes leading to sporadic PD begin many years before the appearance of the characteristic motor symptoms, and that additional neuronal fields and neurotransmitter systems are also involved in PD, including olfactory structures, amygdala, caudal raphe nuclei, locus coeruleus, and hippocampus. Accordingly, adrenergic and serotonergic neurons are also lost, which seems to contribute to the anxiety in PD. Non-motor features of PD usually do not respond to dopaminergic medication and probably form the major current challenge in the clinical management of PD. Additionally, most studies performed with animal models of PD have investigated their ability to induce motor alterations associated with advanced phases of PD, and some studies begin to assess non-motor behavioral features of the disease. The present review attempts to examine results obtained from clinical and experimental studies to provide a comprehensive picture of the neurobiology and current and potential treatments for anxiety in PD. The data reviewed here indicate that, despite their high prevalence and impact on the quality of life, anxiety disorders are often under-diagnosed and under-treated in PD patients. Moreover, there are currently few clinical and pre-clinical studies underway to investigate new pharmacological agents for relieving these symptoms, and we hope that this article may inspire clinicians and researchers devote to the studies on anxiety in PD to change this scenario.

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1. Introduction

The prevalence of Parkinson's disease (PD) is generally estimated at 0.3% of the entire population and at about 1% of people over 60 years of age (Mayeux, 2003). Since the incidence of the disease increases with age (the most important risk factor), it is likely that the number of people suffering from PD will rise steadily in the future. Overall, the annual economic impact of PD in the United States is estimated at $10.8 billion, 58% of which is related to direct medical costs (O'Brien et al., 2003).

Classically, PD is considered as a movement disorder, and its diagnosis is based on the presence of a set of cardinal motor signs (e.g. rigidity, bradykinesia, rest tremor, and postural reflex distur-bance). These symptoms of PD mainly result from the progressive and profound loss of neuromelanin-containing dopaminergic neurons in the substantia nigra pars compacta (SNpc) with

presence of eosinophillic, intracytoplasmic, proteinaceous inclusions termed as Lewy bodies and dystrophic Lewy neurites in surviving neurons (Hirsch et al., 1988).

Dopamine (DA)-replacement therapy has dominated the treatment of PD since the early 1960s and although the currently approved anti-parkinsonian agents offer effective relief of the motor deficits, especially in the early/moderate stages of the disease, they have not been found to alleviate the underlying dopaminergic neuron degeneration and drug efficacy is gradually lost (Allain et al., 2008). Moreover, the dopaminergic therapy in PD is based on the importance of nigral dopaminergic cell loss, the ensuing striatal DA depletion, and the onset of motor symptoms. However, there is now considerable evidence showing that the neurodegenerative processes leading to sporadic PD begin many years before the appearance of the characteristic motor symptoms, and additional neuronal fields and neurotransmitter systems are also involved in PD, including the anterior olfactory structures, amygdala, dorsal motor nucleus of vagus, caudal raphe nuclei, *locus coeruleus*, autonomic nervous system, hippocampus, and cerebral cortex (Braak et al., 2004). Accordingly, cholinergic, adrenergic and serotonergic neurons are also lost, which seems to contribute to the appearance of non-motor symptoms of PD encompassing olfactory and memory impairments, sleep abnormalities, anxiety and depression, as well as gastrointestinal disturbance, which in many cases precede the manifestation of motor symptoms (Chaudhuri et al., 2006).

Remarkably, systematic reviews have indicated non-motor symptoms (including depression and anxiety) as major factors in determining health-related quality of life, progression of disability, and nursing home placement in PD patients (Den Oudsten et al., 2007; Soh et al., 2011). Moreover, non-motor features of PD usually do not respond to dopaminergic medication and probably form the major current challenge faced in the clinical management of PD (Chaudhuri et al., 2006). As illustrated in Fig. 1, over the past 30 years (and particularly in the last decade) an increasing number of studies has been devoted to the investigation of anxiety in both PD patients and animal models of PD.

Theories related to the etiology of anxiety symptoms in PD argue that they are "reactive" and secondary to the psychosocial stress of a chronic disease and the associated disability. On the other hand, there is increasing evidence that psychological symptoms could be a result from neurochemical changes that occur due to the neurodegeneration even during early pre-motor phases of PD. In many cases, anxiety disorders may precede or be accompanied by depression and, in such cases, even when the depression is treated anxiety may remain (Marsh, 2000). However, despite their high prevalence, anxiety disorders are often under-diagnosed and under-treated in PD patients (Leentjens et al., 2011a).

Interventions for psychological symptoms in PD patients received not as much attention as that for motor symptoms in PD patients, and thus, much of the information and management strategies presented are based on observational studies, expert opinion, or clinical guidelines for a condition in patients without PD, but few have been studied extensively in randomized controlled trials (RCTs).

On the other hand, a valid animal model is helpful for screening potential drugs in pre-clinical study and for developing new therapeutic methods for PD. In this context, recent pre-clinical findings have indicated that, through the use of low doses or specific routes of

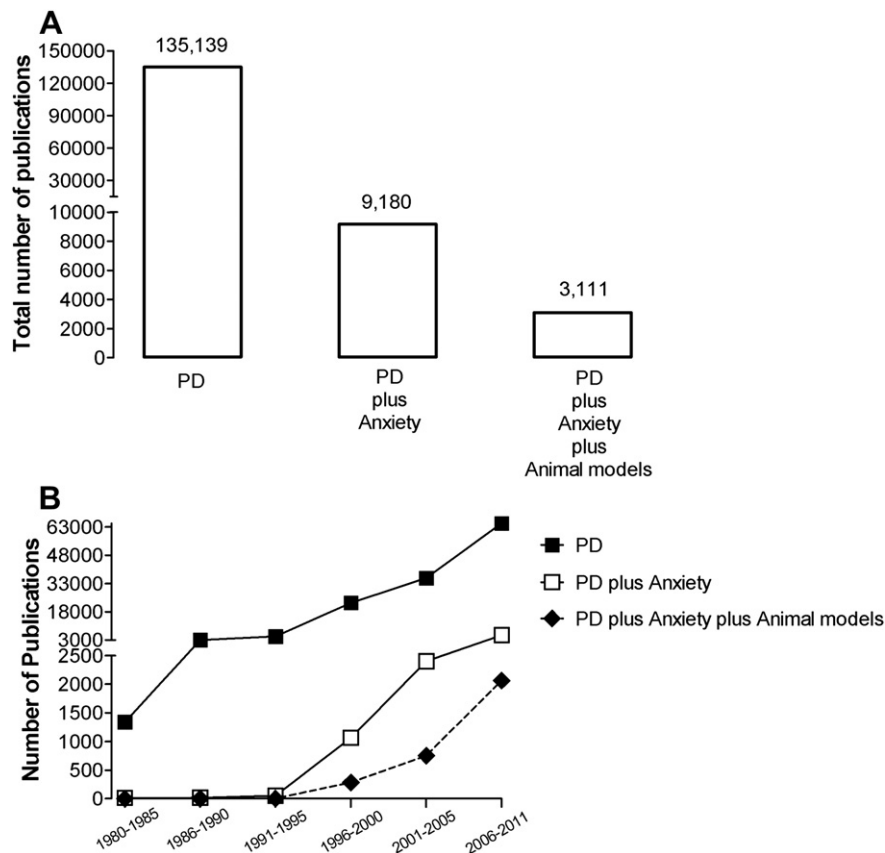Fig. 1. Number of publications containing the keywords "Parkinson's disease" (PD), "PD plus Anxiety", and "PD plus Anxiety plus Animal Models" found in the SCOPUS databases. Panel A illustrates the total number of publications (time spam "all years") obtained for the queries. A time-line concerning the publications from year 1980 until July 15th of the year 2011 obtained from SCOPUS databases is shown in panel B.

administration (e.g., intranigral, intrastriatal, intranasal), some toxins widely used to induce experimental parkinsonism such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) do not cause, at least at selected time windows, gross motor alterations that would preclude assessment of other functions, and thus they may be useful for the study of anxiety-like behaviors in laboratory animals.

Therefore, the present review attempts to examine results obtained from clinical and experimental studies to provide a comprehensive picture of the neurobiology and current and potential treatments for anxiety in PD.

2. The neurobiology of anxiety in Parkinson's disease

Data obtained from large-scale epidemiological studies of psychiatric illnesses suggest that anxiety disorders affect 15.7 million people in the United States annually and 30 million people at some time in their lives (Lépine, 2002). Anxiety disorders typically begin in early adulthood and trends to have a chronic and persistent course that frequently presents co-morbidly with other conditions (about 90% of these patients have at least one co-morbid lifetime psychiatric disorder) (Pollack, 2009). The prevalence of anxiety in PD is disparate, with studies reporting rates from 5% (Lauterbach and Duvoisin, 1991) to 69% (Kulisevsky et al., 2008). About 30% of patients suffering from depression in PD also experienced panic disorder, and an additional 11% expressed generalized anxiety, compared to 5.5% of general population (Nuti et al., 2004). Other authors, however, reported that anxiety disorders occur in approximately 25–35% of PD patients (Dissanayaka et al., 2010; Goetz, 2010; Leentjens et al., 2011a) while Nègre-Pagès et al. (2010) described that half of PD patients have probable/possible anxious symptoms.

Anxiety in PD may represent a psychological reaction to the development of other symptoms (mainly motor disturbance) during the disease's progression. Patients with PD experience considerably higher stress than people without the disease (Ellgring et al., 1990) and they may suffer from social anxiety: patients are afraid of being negatively evaluated in public. Anxiety and social withdrawal may then result. On the other hand, there is increasing evidence that anxiety disorders may be directly related to neurochemical changes in PD. In this context, epidemiological and case–control studies have indicated that anxiety may be one of the earliest manifestations in PD (Bower et al., 2010; Shiba et al., 2000; Weisskopf et al., 2003). For instance, the Health Professionals Follow-up study showed that "phobic anxiety" was a significant risk factor for the development of PD (Weisskopf et al., 2003), and the Minnesota Multiphasic Personality Inventory's composite neuroticism score also showed that patients with high anxiety were at an increased risk for PD (Bower et al., 2010). Therefore, anxiety and PD could share some underlying biological mechanisms that lead to them at any stage of disease including pre-motor phase.

The relationship between dopaminergic transmission and clinical anxiety disorders is complex and poorly understood (for review see Millan, 2003). However, there is evidence that abnormalities in dopaminergic transmission are associated with anxiety in PD. For instance, social phobia, which is common in parkinsonian patients, is associated with a sustained suppression both of dopaminergic transmission and of activity at DA receptors (Grant et al., 1998; Schneier et al., 2000; Stein et al., 2002; Tiihonen et al., 1997). An association between decreased binding to DA transporters in the left ventral striatum and depressive and anxious symptoms was reported in some studies (Remy et al., 2005; Weintraub et al., 2004). Functional magnetic resonance imaging studies have indicated the involvement of a perturbation of dopaminergic input to the amygdala in the abnormal emotional express in PD patients (Benke et al.,

1998; Tessitore et al., 2002). DA-depleted rodents manifest increased anxiety-like behaviors (Eskow Jaunarajs et al., 2010; Tadaiesky et al., 2008; Taylor et al., 2009). Of high importance, several studies have pointed that the onset of anxiety symptoms predates the emergence of motor impairments in PD patients (Bower et al., 2010; Shiba et al., 2000; Weisskopf et al., 2003) as well as in pre-clinical animal models of PD (Branchi et al., 2008; Eskow Jaunarajs et al., 2010; Tadaiesky et al., 2008; Taylor et al., 2009), since motor symptoms typically do not manifest until about 70% of nigral DA neurons have been lost. Therefore, the anxiety symptoms may be more sensitive to DA depletion.

There are connections between the brain areas involving emotional anxiety and fear and those controlling postures (Balaban and Thayer, 2001). In particular, the amygdala and associated limbic structures play a pivotal role in the acquisition, modulation and expression of emotions, such as fear and anxiety, and have widespread efferent connections to areas involved in posture, including vestibular nuclei, the reticular formation, and nuclei within the basal ganglia and nucleus accumbens (Balaban and Thayer, 2001; Cardinal et al., 2002). Nevertheless, the exact role of basal ganglia in mediating anxiety and fear responses remains unclear. Some data reveal that dopaminergic medication generally has little effect on improving postural control, particularly during quiet stance (Bloem et al., 1996; Rocchi et al., 2006), but it may improve anxiety and emotional processing impairments in PD (Maricle et al., 1995; Tessitore et al., 2002; Witjas et al., 2002). Moreover, a recent study demonstrated that the postural control of quiet standing in healthy elderly control subjects and PD patients on medication is equally susceptible to the anxiety modulation (Pasman et al., 2011). The authors of this study suggested that high prevalence of anxiety and fear of falling in PD patients need to be taken into account when interpreting balance assessments in these patients (Pasman et al., 2011).

More recently, a group of anxiogenic conditions that have received special attention in PD patients is the impulse control disorders (ICDs). ICDs are characterized by a failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person and others, and supposed to represent the severe end of a spectrum of related disorders in PD sharing poorly or uncontrolled repetitive behaviors, including DA dysregulation syndrome and punding (Weintraub and Potenza, 2006; Weintraub, 2009; Weintraub et al., 2010). Typically, patients feel an increasing sense of tension or excitement before acting out. A sense of relief, pleasure or gratification arises while acting out or shortly thereafter, and the behavior is followed by remorse and guilt. The Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) (APA, 2000) contains pathological gambling, kleptomania, pyromania, intermittent explosive disorder, and trichotillomania as separate diagnostic categories within the ICDs. In addition, several excessive behaviors characterized by difficulties resisting temptations to engage in ultimately harmful behaviors are conceptualized as ICDs not otherwise specified (ICD-NOS), including compulsive buying, pathological skin picking, non-paraphilic compulsive sexual behavior, and pathological internet use (Kuzma and Black, 2005). Especially DA agonists have been implicated in the development of ICDs and related disorders (Ondo and Lai, 2008; Voon et al., 2007; Weintraub et al., 2006). DA D1 and D2 receptors, abundant in the dorsal striatum, are recognized for mediating the motor control by DA, whereas DA D3 receptors are abundant in the ventral striatum and have been associated with both behavioral addictions and substance use disorders (Gerlach et al., 2003). The second generation of non-ergot DA agonists (e.g., pramipexole and ropinirole) have demonstrated relative selectivity for DA D3 receptors compared with D2 and D1 receptors and thus they could influence impulse control (Brewer and Potenza, 2008; Gerlach et al., 2003).

Long-term follow-up studies have shown that discontinuing or decreasing DA agonists administration, even when offset by an increase in L-DOPA treatment, is associated with remission of or marked reduction in ICDs (Bharmal et al., 2010).

In addition, recent evidence suggests that the noradrenergic and serotonergic systems may play a more relevant role in the manifestation of PD-related anxiety than previously thought (Eskow Jaunarajs et al., 2011). According to Braak staging of PD pathology, serotonergic cell loss in the raphe nuclei is evident prior to nigrostriatal dopaminergic degeneration (Del Tredici et al., 2002; Braak et al., 2004). Serotonergic neurons originating in raphe nuclei provide a massive input to corticolimbic structures involved in the control of anxious states, and there are many studies demonstrating that anxiety disorders may be caused by abnormalities in the action of serotonin (5-HT) (see Millan, 2003). Remarkably, Menza et al. (1999) found that patients with PD who carried the short allele of the 5-HT transporter scored significantly higher than non-carriers on anxiety scales. This suggests that genetic factors may play a role in the pathogenesis of anxiety in PD.

Noradrenaline (NA) dysfunction likely also occurs prior to pronounced degeneration of DA neurons (Braak et al., 2004). Ascending noradrenergic projections from the *locus coeruleus* heavily innervate the hippocampus, amygdala, periaqueductal gray, cortex, hypothalamus and essentially all corticolimbic regions involved in integrating the response to anxiety (see Millan, 2003). Due to NA cell loss in the *locus coeruleus* of PD patients, significant changes in the expression of NA receptors and transporters may prompt the development or exacerbation of anxiety. Regardless of their history of anxiety, PD patients exhibit susceptibility to panic attacks induced by yohimbine (an antagonist of α2-adrenergic receptors), similar to those in psychiatric patients with panic disorder (Richard et al., 1999). Furthermore, lower DA/NA transporter binding in the *locus coeruleus* is correlated with increased incidence of anxiety in PD patients (Remy et al., 2005). While plasma NA levels are elevated in de novo PD patients (Ahlskog et al., 1996), lower levels of dopamine β-hydroxylase, the enzyme responsible for hydroxylation of DA to NA, have been observed in the cerebrospinal fluid of L-DOPA-treated PD patients (Nagatsu and Sawada, 2007; O'Connor et al., 1994) and imply that L-DOPA treatment may alter NA levels.

Other neurotransmitter systems including those of gamma-aminobutyric acid (GABA) and glutamate have been implicated in the pathogenesis of anxiety disorders (Millan, 2003), and abnormalities of these neurotransmitter systems have been shown in patients with PD (Gardoni et al., 2010; Kashani et al., 2007; Lanoue et al., 2010). Moreover, pre-clinical studies and clinical pharmacological studies have suggested that drugs that modulate the activity of GABA and glutamate neurotransmitter systems have a potential to treat anxiety disorders in PD (Chen et al., 2011a,b; Ho et al., 2011; Marsh and Berk, 2003; Valenti et al., 2003). However, the involvement of GABA and glutamate in neurobiology of anxiety in PD is not yet clear, and this constitutes a very interesting field for futures studies.

A better understanding on the neuronal networks involving emotional and motor control and the role of neurotransmitters and their receptor subtypes in the modulation of such responses will facilitate developing therapeutic methods for anxiety symptoms in PD and ultimately improve life quality of these patients.

3. Clinical findings of anxiety in Parkinson's disease

Anxiety may cause a significant deterioration of parkinsonian symptoms (Routh et al., 1987); however, it may go unnoticed unless expressly sought and can have a marked effect on motivation and rehabilitation. Panic disorder, generalized anxiety disorder, and social phobia are the most common anxiety disorders reported in PD patients (Dissanayaka et al., 2010). There is a frequent co-morbidity between anxiety and depressive disorders in PD, ranging from 14 to 26% (Dissanayaka et al., 2010; Leentjens et al., 2011a; Menza et al., 1993). Anxiety and depression may be difficult to distinguish; however, unlike depression, a core feature of anxiety is the presence of apprehension, fear, or worry. Although there is an increasing number of clinical reports addressing the association between anxiety disorders and idiopathic PD or its treatments (see Table 1), as highlighted by a recent review by Leentjens et al. (2011a), anxiety disorders remain under-studied in PD. This cannot be justified by their prevalence or by their impact on patients' quality of life.

Gotham et al. (1986) assessed 189 patients with PD, 57 patients with arthritis, and 100 elderly normal controls with the Beck depression inventory, the Beck hopelessness scale, and the Spielberger anxiety index. The patients with PD scored significantly higher than the normal controls on these assessment scales but did not differ from those with arthritis. Stein et al. (1990) systematically evaluated 24 patients with idiopathic PD for the presence of Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R axis I syndromes. They found that 9 of 24 parkinsonian patients had anxiety symptoms. Menza and Mark (1994) studied 104 patients with PD and 61 medical control subjects with similar disability for symptoms of anxiety and depression. All patients completed the Zung self-rating anxiety scale and PD patients scored significantly higher than control patients.

More recently, Negrè-Pagès et al. (2010) assessed anxiety and depressive symptoms in 450 ambulatory non-demented PD patients and 98 patients with other disorders than PD using the Hospital Anxiety and Depression Scale (HADS) and their findings indicated that patients with possible/probable anxious signs (HADS-A > or = 8) were more prevalent in PD (51%) than in the others patients (29%). In a recent cross-sectional study with 342 patients suffering from idiopathic PD, Leentjens et al. (2011b) reported that 34% of the subjects met the DSM-IV criteria for at least one anxiety disorder; 11.8% met criteria for multiple anxiety disorders; and 11.4% had clinically relevant anxiety symptoms without meeting the criteria for any specific anxiety disorder (Leentjens et al., 2011b). Although this is in the same range as the prevalence reported in earlier studies, the relative proportion of the different anxiety disorders varies widely between studies. For instance, early studies found an increase in episodic anxiety disorders (e.g., panic disorder) in PD (Goetz, 2010), while more recent studies observed an increased

Table 1
Summary of the clinical findings of anxiety disorders in Parkinson's disease (PD).

References	Main findings
Bower et al., 2010; Shiba et al., 2000; Weisskopf et al., 2003	Onset at any stage of PD, even as a pre-motor manifestation
Negrè-Pagès et al., 2010; Leentjens et al., 2011a	Prevalence up to 50% of clinically significant anxiety
Dissanayaka et al., 2010	Panic disorder, generalized anxiety disorder and social phobia are the most common specific disorders
Dissanayaka et al., 2010; Leentjens et al., 2011a; Menza et al., 1993	Co-morbidity with depression is frequent
Menza et al., 1990; Nissenbaum et al., 1987; Racette et al., 2002; Siemers et al., 1993	Possibly more common during the "off phase"
Eskow Jaunarajs et al., 2011	Unclear relationship with anti-parkinsonian medication
Remy et al., 2005	Decreased binding to dopamine and noradrenaline transporters in limbic areas

association with non-episodic anxiety such as generalized anxiety disorder (Dissanayaka et al., 2010; Leentjens et al., 2011a,b) (Table 1).

As mentioned before, ICDs are another group of anxiogenic conditions that have received special attention in PD in the last years (Weintraub and Potenza, 2006). Prevalence estimates in the general population of the United States have been reported as approximately 1% for pathologic gambling (Potenza et al., 2001), 5% for compulsive sexual behavior (Black et al., 1998), and 2%–8% for compulsive buying (Black et al., 1998). Recent observational studies suggest that ICDs, particularly pathologic gambling (Dodd et al., 2005; Driver-Dunckley et al., 2003; Gschwandtner et al., 2001; Molina et al., 2000; Seedat et al., 2000) and compulsive sexual behavior (Klos et al., 2005), frequently co-occur with PD. The prevalence of ICDs in PD is not precisely known. Most studies have focused on problem or pathologic gambling, and estimated frequencies in PD from published case series range from 0.5% (Molina et al., 2000) to 4.9% (Driver-Dunckley et al., 2003). These values may underestimate the real frequencies, since individuals with ICDs may be hesitant to acknowledge symptoms. As highlighted by Weintraub and Potenza (2006), determining the extent to which the observed frequencies of various ICDs in PD are higher or lower than in the general population requires further examination with larger, age-matched, sex-matched, and medical morbidity-matched community samples.

Of high importance, the relationship between anxiety and motor disturbance in PD remains controversial. While some studies indicate that anxiety is related to severity of PD (especially, posture instability and gait dysfunction) (Leentjens et al., 2011a; Siemers et al., 1993), other studies have found that anxiety was not correlated with severity of motor symptoms (Menza et al., 1993; Starkstein and Leiguarda, 1993; Stein et al., 1990). Moreover, several studies indicate that anxiety is more prevalent in the "off phase" of L-DOPA treatment, when the patients fail to response to the treatment of motor symptoms in PD (Menza et al., 1990; Nissenbaum et al., 1987; Racette et al., 2002; Siemers et al., 1993). However, some authors have not found this phenomenon (Lauterbach and Duvoisin, 1991; Stein et al., 1990).

Another debatable issue in the literature is whether anti-parkinsonian medications are responsible for symptoms of anxiety in PD. As recently reviewed by Eskow Jaunarajs et al. (2011), while some groups have reported significant improvements in anxiety upon L-DOPA treatment (Funkiewiez et al., 2006; Maricle et al., 1995; Stacy et al., 2010), others have asserted that there is no such improvement or that L-DOPA exacerbates anxiety (Damásio et al., 1971; Richard et al., 1996; Vázquez et al., 1993). Moreover, Lang et al. (1982) reported anxiety in 5 of 26 patients when the DA receptor agonist pergolide was added to their treatment regimen. However, Menza et al. (1993) found no differences in measures of anxiety between controls and patients receiving pergolide. Leentjens et al. (2011a) found that the use of monoamine oxidase B (MAO-B) inhibitors is associated with reduced anxiety disorders in PD patients, although Negrè-Pagès et al. (2010) did not find any difference in anxiety symptom frequency between MAO-B inhibitors users and non-users. Therefore, the relationship of anti-parkinsonian medication and anxiety in PD needs further clarification.

4. Experimental findings of anxiety in Parkinson's disease

As mentioned in the previous sections of this review, PD seems to be a multidimensional disease and, besides motor deficits, it is associated with a number of non-motor symptoms including anxiety that can precede the classical motor features of PD by years and contribute substantially for the loss of quality of life in PD patients (Chaudhuri et al., 2006; Reijnders et al., 2009). Animal models are an invaluable tool for studying the pathogenesis and progression of human diseases, as well as for testing new therapeutic intervention

strategies. PD is one of human diseases that do not occur spontaneously in animals. However, the characteristics of this disease can be induced in laboratory animals through the administration of different compounds such as reserpine, 6-OHDA, MPTP, and rotenone (Beal, 2001; Dawson, 2000; Gerlach and Riederer, 1996). Although these models have undoubtedly contributed to a better understanding of many features of PD, most studies have focused on the ability of these models to induce nigrostriatal pathway damage and motor alterations associated with advanced phases of PD. However, there is no well-accepted PD model with non-motor symptoms.

As recently highlighted by Taylor et al. (2010), since research continues to unmask PD as a multi-system disorder, animal PD models should also present non-motor behavioral features of this disease. In this context, recent pre-clinical findings have indicated that through the use of low doses and/or specific routes of administration (e.g., intranigral, intrastriatal, intranasal), some toxins widely used to induce experimental parkinsonism such as MPTP and 6-OHDA induce a moderate loss of the nigral dopamine neurons (40–60%) resulting in sensorial, emotional and memory deficits with no major motor impairments. Table 2 summarizes the findings of anxiety-like behaviors reported in previous studies using diverse animal models of PD (for a previous review, see Eskow Jaunarajs et al., 2011).

In a pioneer study, Branchi et al. (2008) undertook a first attempt to characterize emotional behaviors following partial DA depletion made by bilateral intrastriatal 6-OHDA (10.5 μg) injection in rats. The authors reported that 6-OHDA-lesioned rats displayed an increased exploration of the open arms of the elevated plus maze (EPM) test as well as reduced offensive behavior and increased propensity to interact socially in the social interaction test, indicating an anxiolytic-like effect after 6-OHDA lesion. Interestingly, in a rather similar study, Tadaiesky et al. (2008) described the opposite effects (i.e., reduction in the exploration of the open arms of the EPM) after a partial degeneration of dopaminergic neurons achieved by bilateral infusion of 6-OHDA (12.5 μg) in the striatum of rats at week 3 after the lesion. Therefore, these findings suggest increased anxiety-like behaviors, which fit better with hypotheses of PD-like non-motor change predicted from the clinical literature. The infusion of 6-OHDA in the striatum also resulted in a partial depletion of striatal DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-HT, in addition to an increase in NA levels, possibly due to a compensatory response to DA reduction (Tadaiesky et al., 2008). Moreover, Tadaiesky et al. (2008) suggested that the anxiogenic response elicited by 6-OHDA could be associated with the DA depletion in the prefrontal cortex, since these alterations were observed only after three weeks of 6-OHDA administration. This hypothesis is supported by previous evidence that 6-OHDA injected directly into the prefrontal cortex induces a significant anxiogenic effect in rats evaluated in the EPM (Espejo, 1997).

Corroborating these findings, Chen et al. (2011a,b) recently reported anxiogenic responses of rats evaluated in the EPM and social interaction tests following bilateral injection of 6-OHDA into the dorsal striatum that were accompanied by a small loss of dopaminergic neurons in the SNpc (31.5%) and VTA (20%). Moreover, Eskow Jaunarajs et al. (2010) reported an increase in anxiety-like behaviors in hemiparkinsonian rats evaluated in locomotor chambers and in the social interaction test after unilateral infusion of 6-OHDA (12.5 μg) into the medial forebrain bundle (MFB). Furthermore, in a series of recent studies, Ho's research group demonstrated that rats infused bilaterally with MPTP directly into the SNpc displayed reduced exploration of the open arms of the EPM indicating increased anxiety-like levels. However, the number of enclosed-arm entries and the total distance traveled in the EPM test, which are commonly used to measure general activity, were not altered by intranigral MPTP administration (Ho et al., 2011; Sy et al., 2010; Wang et al., 2009) (see Table 2).

Table 2
Summary of the anxiety-like responses described in animal models of Parkinson's disease.

Specie/Strain	Parkinson's disease model	Behavioral test - Time after lesion	Effect	References
Rat/Wistar	Striatal 6-OHDA (10.5 μg) – bilateral	Elevated plus maze – 5 weeks	Anxiolytic	Branchi et al., 2008
		Social interaction – 7 weeks	Anxiolytic	
Rat/Wistar	Striatal 6-OHDA (12 μg) – bilateral	Elevated plus maze – 3 weeks	Anxiogenic	Tadaiesky et al., 2008
Rat/Sprague-Dawley	Striatal 6-OHDA (10.5 μg) – bilateral	Elevated plus maze – 15–17 days	Anxiogenic	Chen et al., 2011a,b
		Social interaction – 17–19 days	Anxiogenic	
Rat/Sprague-Dawley	MFB 6-OHDA (12 μg) – unilateral	Locomotor chambers – 7 weeks	Anxiogenic	Eskow Jaunarajs et al., 2010
		Social interaction – 7 weeks	Anxiogenic	
Rat/Wistar	SNpc MPTP (1 μmol) – bilateral	Elevated plus maze – 11 days	Anxiogenic	Wang et al., 2009; Ho et al., 2011
Rat/Wistar	SNpc MPTP (1 μmol) – bilateral	Elevated plus maze – 25 days	Anxiogenic	Sy et al., 2010
Mouse/C57BL/6	Intraperitoneal MPTP (4 × 20 mg/kg, 2 h apart)	Light-dark preference –7or30days	No effect	Vucković et al., 2008
		Hole-board –8or31days	No effect	
Mouse/C57BL/6	Intraperitoneal MPTP (4 × 20 mg/kg, 2 h apart)	Marble burying –35days	Anxiogenic	Gorton et al., 2010
		Elevated plus maze –36days	No effect	
Mouse/C57BL/6	Intranasal MPTP (1 mg/nostril)	Elevated plus maze –7days	No effect	Prediger et al., 2010
Mouse/C57BL/6	Striatal 6-OHDA (8 μg) – bilateral	Elevated plus maze –4 weeks	Anxiolytic	Branchi et al., 2010
		Open field – 4 weeks	No effect	
Mouse	Parkin-deficient mice	Open field	Anxiogenic	Zhu et al., 2007
		Light-dark preference	Anxiogenic	
Mouse	A53T synuclein transgenic mice	Elevated plus maze	No effect	George et al., 2008
		Open field	Anxiogenic	
Mouse	DJ-1 knockout mice	Elevated plus maze	No effect	Chandran et al., 2008
Mouse	VMAT-2 deficient mice	Elevated plus maze	Anxiogenic	Taylor et al., 2009
		Open field	Anxiogenic	

6-OHDA = 6-hydroxydopamine; MFB = medial forebrain bundle; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SNpc = substantia nigra pars compacta; VMAT-2 = vesicular monoamine transporter.

It is worth mentioning that the development of these models in the mouse species will be relevant for future studies aimed at combining chemical lesions and genetic manipulations. However, the findings described so far by the studies addressing anxiety-like behaviors in neurotoxin-induced mouse models of PD have been inconsistent (Table 2). Vucković et al. (2008) administered MPTP (4 i.p. injections of 20 mg/kg at 2-h intervals) to C57BL/6 mice, and independent groups of animals were evaluated at either 7 or 30 days post-lesioning on associative memory, conditioned fear, and affective behavioral tasks. Although mice at both 7 and 30 days post-MPTP administration displayed increased fear extinction, no changes in anxiety-like behaviors were observed in the light–dark preference or hole-board tests (Vucković et al., 2008). Interestingly, using the same regime of MPTP treatment described above, Gorton et al. (2010) reported recently that MPTP-treated C57BL/6 mice displayed increased anxiety-like responses in the marble-burying test, but MPTP failed to elicit similar anxiogenic responses in the EPM test. In this regard, defensive burying represents an active coping strategy in response to a discrete threat. By contrast, anxious behavior in the EPM is expressed as a passive avoidance response to a potential threat. Therefore, different brain circuits may regulate responses to these two challenges (Hakvoort Schwerdtfeger and Menard, 2008) and this should be taken into account in further studies addressing anxiety responses in animal models of PD.

Prediger et al. (2010) demonstrated that, despite the development of clear sensorial and cognitive impairments, C57BL/6 mice infused intranasally with MPTP (1 mg/nostril) did not display an increase in anxiety-like responses as evaluated in the EPM. In contrast with the data reviewed above, Branchi et al. (2010) showed a significant reduction in anxiety-like behavior in the EPM after bilateral striatal injection of a moderate 6-OHDA dose (8 μg) in C57BL/6 mice. Interestingly, no difference was found for the time spent by these animals in close proximity to the walls (i.e., thigmotaxis) in the open field, another widely used parameter for the study of anxiety-related behaviors in rodents, and the causes for theses inconsistencies need to be further investigated.

In addition, the findings obtained to date in genetic mouse models of PD are also controversial (Table 2). For instance, younger vesicular monoamine transporter-2 (VMAT-2)-deficient mice spend a greater percentage of their time in the closed arms of the EPM as compared to age-matched wild-type animals, thus exhibiting an anxiety-like phenotype (Taylor et al., 2009). However, DJ-1 knockout mice were found to not exhibit an anxiety-like phenotype, showing no significant difference in the exploration of the open arms of the EPM in comparison to their wild-type littermates (Chandran et al., 2008).

Although transgenic mice over-expressing α-synuclein A53T did not show an anxiety-like phenotype in the EPM, these animals displayed a selective anxiety-like phenotype in the open field test as indicated by reduced habituation and increased thigmotaxis compared to α-synuclein knockout and wild-type mice (George et al., 2008). Moreover, Parkin-deficient mice also exhibit increased thigmotaxic behavior associated with decreased horizontal locomotion distance in the open field in comparison to wild-type mice (Zhu et al., 2007). In addition, it is interesting to note that both young adult and aged Parkin knockout mice were found to spend significantly less time in the illuminated side of the light–dark chamber and to make fewer transitions between the two compartments than control littermates (Zhu et al., 2007).

Taken together, these results, although conflicting at first glance, are indicative of a trend toward an anxiety-like phenotype characterized in different animal models of PD, thus in line with some behavioral signs concerning domains affected during the early phase of PD.

5. Current and new treatments for anxiety in Parkinson's disease

To date, no specific pharmacological treatment for anxiety disorders in PD patients, and most of the management strategies used are based on observational studies, expert opinion, or clinical guidelines for anxiety disorders in patients without PD (Walsh and Bennett, 2001). Table 3 summarizes the main drugs utilized in the treatment of anxiety disorders in PD patients.

In patients who appear to be anxious as a result of anti-parkinsonian medication, dose reduction or replacement by a different medication may be the best approach (Walsh and Bennett, 2001). When anxiety symptoms are temporally correlated to the "off state", it is essential to treat the motor complications before treating anxiety (Schrag, 2004). Thus, it is necessary

Table 3
Drugs effective for the treatment of anxiety disorders in Parkinson's disease. See text for references and additional information.

Drug	Comments
BDZs with short-half-life	• Administered during short periods of time
Alprazolam	• More effective than SSRIs
Lorazepam	• High potential for side effects such as sedation, increase risk of falls and cognitive impairments
Oxazepam	
Anxiolytic non-BDZs	• Low doses recommended
Buspirone	• Reduces L-DOPA-induced dyskinesias
	• In high doses can worsen motor function and cause nausea and insomnia
Adjustments in dopamine therapies	• Effective to adjust motor function
Dopamine agonists L-dopa	• Strategy to allow initiates the anxiolytic therapy
TCAs	• Alternative for patients non-responsive to SSRIs and BDZs
Desipramine	• Avoided in patients considered at risk of suicide
SSRIs – Citalopram	• Used only if depression is also presented
NSRIs – Venlafaxine	• Well tolerated
	• Can cause an initial increase in anxiety, insomnia, nausea and sexual dysfunction
Others	• In low doses show anxiolytic effect
Clozapine	• Requires hematological monitoring due to the risk of inducing agranulocytosis

BDZs = benzodiazepines; TCAs = tricyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors; NSRIs = noradrenaline selective reuptake inhibitors.

to adjust the anti-parkinsonian therapy before initiating the administration of anxiolytics (Ferreri et al., 2006).

Benzodiazepines (BDZs) are a therapeutic option for the management of anxiety in PD, but special care must be taken. BDZs are thought to exert their anxiolytic effect by binding to the type A gamma-aminobutyric acid (GABAA) receptors and potentiating inhibitory neurotransmission (Möhler et al., 2002). The elders may be more sensitive to drug-induced side effects, such as, sedation, cognitive impairment, confusion and falls (Walsh and Bennett, 2001). BDZs with shorter half-life such as alprazolam, lorazepam or oxazepam are preferable to avoid drug accumulation and minimize side effects (Marsh and Berk, 2003). Another important issue is the risk of abuse and dependence, as well as withdrawal syndrome, particularly in the case of short-half-life BDZs. Thus, the use of BDZs should be limited to a period of two weeks (Hanagasi and Emre, 2005) (Table 3).

The non-benzodiazepine anxiolytic drug buspirone has been also utilized to treat anxiety in PD. Buspirone is a partial agonist of the 5-HT receptors type 1A (5-HT1A). The 5-HT1A receptors are located both pre-synaptically in the raphe nuclei (somatodendritic autoreceptors), where they act as body autoreceptors to inhibit the firing rate of 5-HT neurons, and post-synaptically in the limbic and cortical regions, where they also attenuate firing activity (Blier and Ward, 2003; Marsh and Berk, 2003). The anxiolytic action of buspirone may result from the decrease in the activation of 5-HT receptors types 2A and 2C (5-HT2A/2C), thus mimicking the effects of ritanserin, a post-synaptic 5-HT2A/2C receptor antagonist (Bond et al., 2003). Clinical response in anxiety is usually observed only after two weeks of administration. When used in low doses, buspirone shows anxiolytic effects and also reduces L-DOPA-induced dyskinesias, without causing sedation or motor impairment (Bonifati et al., 1994). Although well tolerated, buspirone in high doses can worsen motor symptoms of PD, in addition to causing nausea and insomnia (Ferreri et al., 2006; Ludwig et al., 1986).

Selective serotonin reuptake inhibitors (SSRIs) such as citalopram and sertraline, and NA and 5-HT reuptake inhibitors (NSRIs) such as venlafaxine raise the levels of these neurotransmitters in the synaptic cleft and thus improving NA and 5-HT neurotransmission that is disrupted in PD. The SSRIs and NSRIs can be used to treat anxiety in PD, but some clinicians use them only when depression is associated (Ferreri et al., 2006). These drugs are well tolerated, but can produce an initial increase in anxiety, insomnia, nausea, and sexual dysfunction. However, venlafaxine should be avoided by patients with cardiac disease, electrolyte imbalance, and hypertension (Baldwin et al., 2005).

The use of low doses of tricyclic antidepressants (TCAs) represents an alternative treatment for anxiety in PD patients that do not respond to BDZs and SSRIs (Lieberman, 1998). Although the exact mechanism of action of TCAs in the anxiety relief in PD patients has not been fully elucidated, it is known that TCAs increase the synaptic levels of NA and 5-HT by blocking their reuptake (Kessel and Simpson, 1995). However, TCAs should be avoided in patients considered at risk of suicide due to their high toxic potential in cardiovascular and CNS functions (Baldwin et al., 2005). Clozapine, an atypical antipsychotic, elicited anxiolytic effects in parkinsonian patients when evaluated in low doses in a retrospective clinical study. However, 23% of patients showed adverse effects or failure during clozapine treatment (Hanagasi and Emre, 2005; Trosch et al., 1998). Moreover, clozapine requires hematological monitoring during its use due to the risk of agranulocytosis, which is an uncommon but potentially lethal side effect.

There is increasing evidence that dysfunction of glutamatergic activity may be involved in the neurodegeneration as well as motor and non-motor symptoms observed in PD (for review see Gardoni et al., 2010). Thus, drugs modulating the function of glutamatergic receptors may have beneficial effects in PD therapy. In this context, interesting studies have demonstrated that D-cycloserine, a partial agonist of the glycine binding site of the N-methyl-D-aspartate (NMDA) receptor, improves mnemonic impairments and anxiety-like behaviors observed in MPTP-lesioned monkeys (Schneider et al., 2000) and rats (Ho et al., 2011; Wang et al., 2010). Indeed, pre-clinical studies have suggested that drugs that modulate the activity of metabotropic glutamate receptors (mGluRs) have a potential to treat anxiety disorders (Chojnacka-Wojcik et al., 2001) as well as PD (Dawson et al., 2000; Marino et al., 2003). A recent study evaluated the effects of 2-methyl-6-(phenylethynyl)-pyridine (MPEP), a mGluR5 antagonist, on anxiety-related behaviors evaluated in the EPM and the electrical activity of neurons of basolateral amygdala (BLA) in rats injected bilaterally with 6-OHDA. Rats lesioned with the neurotoxin displayed anxiety-like behavior in the EPM and decreased electrical activity of neurons in the BLA. The chronic systemic treatment with MPEP produced anxiolytic effects and normalized the firing rate of neurons in the BLA of lesioned rats (Chen et al., 2011a).

In addition, the development of new drugs that have action on the allosteric sites of mGluR seems to be a promising approach, because these substances do not directly activate the receptors, but act enhancing or inhibiting glutamate-induced activation (Marino and Conn, 2006). These compounds have demonstrated a diversified pharmacology acting as agonists, inverse agonists and even antagonists for other allosteric modulators (Marino and Conn, 2006).

Several pre-clinical studies have shown that positive allosteric for mGluR2 (Galici et al., 2005) and negative allosteric for mGluR5 (Cosford et al., 2003) have anxiolytic characteristics. Moreover, positive allosteric modulators for mGluR4 have shown in pre-clinical studies to reduce the transmission action of GABAergic inhibitory pathways in the striatum-pallidal, becoming interesting substances for use in PD (Valenti et al., 2003). However, pre-clinical studies are needed to elucidate the role of these receptors in anxiety and non-motor symptoms in PD.

Despite the increasing knowledge of the last years, further investigations about effective treatments for anxiety in PD are certainly required (Zesiewicz et al., 2010). However, it is important to emphasize that currently there are few pre-clinical studies addressing non-motor symptoms including anxiety in animal models of PD and, unfortunately, currently there are no clinical trials being conducted to investigate new pharmacological agents for the relief of anxiety disorders associated specifically with PD.

6. Conclusion

The data reviewed here indicate that anxiety symptoms deteriorate life quality of patients with PD. However, despite their high prevalence, anxiety disorders are often under-diagnosed and under-treated in PD patients. Theories related to the etiology of anxiety symptoms in PD argue that they are "reactive" and secondary to the psychosocial stress of a chronic disease and the associated disability. On the other hand, there is increasing evidence that anxiety and PD could share some underlying biological mechanisms that lead to them occurring at any stage of the disease, including the pre-motor phase. Although previous PD studies focused mainly on neuroprotective agents and attempted to prevent the progression of neurodegeneration, it is also important to establish new treatments for both motor and non-motor symptoms in PD patients and for improving their life quality. Therefore, we highlighted some drugs that have been used in the treatment of anxiety in PD, but the development and evaluation of new agents are certainly required. In this context, the pre-clinical findings reviewed here indicate that some studies begin to assess non-motor behavioral features of the disease. Unfortunately, there are currently few clinical and experimental studies underway to investigate new pharmacological agents for the relief of anxiety symptoms, and we hope that this article may inspire clinicians and researchers devote to the studies on anxiety in PD to change this scenario.

Acknowledgments

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