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REVIEW

Prevalence, clinical features and treatment of depression in Parkinson's disease: An update

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Abstract

Parkinson's disease (PD) is one of the most prevalent neurodegenerative diseases which typically affects individuals over 65 years. Although the symptomatology is predominantly motor, neuropsychiatric manifestations, *e.g.*, depression, apathy, anxiety, and cognitive impairment occur in the course of the illness and can have a great impact on the quality of life in these patients. Parkinson's disease is commonly comorbid with depression with prevalence rates of depression, generally higher than those reported in general population. Depression in PD is frequently underestimated and consequently undertreated, which have significant effects on the quality of life in these patients. The neurobiology of depression in PD is complex and involves alterations in dopaminergic, serotonergic, noradrenergic and possibly other neurotransmitter systems which are affected in the course of the disease. The tricyclic antidepressants and the selective serotonin reuptake inhibitors are the two classes of antidepressant drugs used for depressive symptoms in PD. Several published studies suggested that both classes are of comparable efficacy. Other serotonergic antidepressants, *e.g.*, nefazodone and trazodone have also been of benefit. Meanwhile, there are limited data available on other drugs but these suggest a benefit from the serotonin and noradrenaline reuptake inhibitors such as mirtazapine, venlafaxine, atomoxetine and duloxetine. Some of the drugs used in symptomatic treatment of PD, *e.g.*, the irreversible selective inhibitors of the enzyme monoamine oxidase-B, rasagiline and selegiline as well as the dopamine receptor agonist pramipexole are likely to have direct antidepressant activity independent of their motor improving action. This would make these drugs an attractive option in depressed subjects with PD. The aim of this review is to provide an updated data on the prevalence, clinical features of depression in subjects with PD. The effects of antiparkinsonian and antidepressant drugs on depressive symptoms in these patients are also discussed.

Key words: Antidepressant drugs; Depression; Serotonin reuptake inhibitors; Parkinson's disease; Tricyclic antidepressants

Core tip: The development of depressive symptoms in Parkinson's disease (PD) has important implications on the daily functioning and quality of life. It is thus important to diagnose and treat depression effectively in these patients. This review aims to discuss the

prevalence, associated factors and drugs used to treat depressive symptoms in PD.

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INTRODUCTION

Idiopathic Parkinson's disease (PD), also known as primary PD or paralysis agitans is the second most common neurodegenerative disease[1]. The disease affects about 1% of the population over the age of 65 years[1,2]. Estimates of the prevalence of PD in Europe vary from 65.6-12500 per 100000, while annual incidence estimates vary from 5-346 per 100000[3,4]. The disease is characterized by a triad of motor symptoms, bradykinesia, rigidity and resting tremors[5]. These symptoms result from the loss of dopaminergic neurons in the substantia nigra pars compacta, with consequent depletion of dopamine in the striatum[6,7]. Other neuronal populations are also affected including serotonergic, noradrenergic and cholinergic systems, which contributes to the development of non-motor symptoms during the course of the disease[8]. Neuropsychiatric symptoms such as depression, apathy, anxiety, sleep disturbances, cognitive impairment occur in the premotor or presymptomatic phase of the disease, as well as in the advanced disease, and can substantially affect the quality of life and activities of daily living[9-11]. The pathophysiology of these symptoms is complex, and reflects the widespread cortical and brainstem pathology and affection of several neurotransmitter pathways[12]. Depression is particularly common in PD patients, is frequently overlooked, and is known to cause significant morbidity[13]. In this paper it is aimed to provide a comprehensive and an updated account on the prevalence and clinical features of depression in subjects with PD. The effect of antiparkinsonian drugs on the course of depression in these patients as well as the tolerability and efficacy of antidepressant medications are presented. Non-pharmacological approaches to treat depression in patients with PD are also discussed.

DEPRESSION

Mood disorders can be subdivided into: (1) unipolar (depressive) disorders; (2) bipolar disorders (formerly manic-depressive illness); and (3) other mood disorders, *e.g.*, psychotic mood disorders, postpartum mood episodes with psychotic features, mood disorders due to a general medical condition, and substance/medication-induced mood disorder[14-16]. The term depression describes a range of mood disturbance in the form of an unhappy or sad mood to markedly decreased mood[16]. There are two diagnostic classifications for depressive disorders. One is the "International Classification of Disorders", 10th edition (ICD-10) system of the World Health Organization[14]. The other is the "Diagnostic and Statistical Manual of Mental Disorder", 5th edition (DSM-V) from the American psychiatric association[15]. The diagnosis of major depression illness depends on the presence of a number of symptoms that include depressed mood, loss of interest or pleasure, significant weight loss, or weight gain, sleep disturbances, psychomotor agitation or retardation, fatigue, loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, or indecisiveness, recurrent thoughts of death or suicidal ideation. One of the symptoms should be either depressed mood or loss of interest or pleasure in usual activities (DSM-V)[15] (Table 1). Symptoms must have been present almost every day for a minimum of 2 wk, represent a change from previous functioning, result in clinically significant distress or impairment in social, occupational, or other important areas of functioning, and are not due to a medication, substance abuse or a general medical condition.

Other types of depressive disorders include disruptive mood dysregulation disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder[15]. Depression might occur in the sitting of medical diseases, especially chronic illnesses such as diabetes mellitus, congestive heart failure, myocardial infarction, rheumatologic disorders. Depressive symptoms can be associated with other psychological diseases, including psychotic disorders[17] or caused by a number of medications including β-adrenoceptor blockers, α-adrenoceptor blockers, digoxin, calcium channel blockers, methyldopa, corticosteroids, psychostimulants , isotretinoin, and interferon-α[18-21]. Depressive symptoms are also a common and often characteristic feature in a number of neurological disorders such as stroke, PD, multiple sclerosis, or epilepsy, in which depression has a strong impact on both quality of life and outcome of the primary neurological disorder[22].

PREVALENCE AND FEATURES OF DEPRESSION IN PD

The estimated lifetime prevalence of depression in the general population is approximately 17%-20%[23,24]. It is estimated that up to 85% of patients will have more than one episode in their lifetimes[23,25]. Moreover, up to 20% of patients with depression will have symptoms lasting for 2 years or more, *i.e.*, chronic depression[23,25]. Prevalence estimates for depression

Table 1 Diagnostic criteria for major depressive episode

Depressed mood most of the day, nearly every day
Markedly diminished interest or pleasure in all or almost all activities
Significant weight loss when not dieting or weight gain
Insomnia or hypersomnia nearly every day
Psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of worthlessness or excessive or inappropriate guilt
Diminished ability to think or concentrate, or indecisiveness
Recurrent thoughts of death or suicidal ideation

Five or more of the symptoms must have been present during the same 2-wk period, represent a change from previous functioning and cause significant distress or impairment in social, occupational or other functioning. One of the symptoms should be either depressed mood or loss of interest or pleasure, significant weight loss or weight gain. Symptoms should be present nearly every day, most of the day are not due to drug or a general medical condition. Criteria adapted from Diagnostic Statistical Manual of Mental Disorders[15].

in PD vary in different studies, but are clearly higher than those reported in general population. Studies in general report a prevalence rate between 21% and 40%[26-32]. Prevalence rates as low as 2.5% and as high as 66% have also been reported[33-52] (Table 2). It has been found that persons treated with antiparkinson drugs had significantly increased rate of subsequent antidepressant drug treatment compared with controls, indicating the high frequency of depression in PD[53]. Moreover, initiation of any antidepressant drug therapy was associated with a higher risk of PD in the 2 years from the beginning of treatment. This suggested that depressive symptoms were an early manifestation of PD, before the appearance of motor symptoms[54]. Jasinska-Myga *et al*[36] found that 72% of patients developed depression within ten years of symptomatic PD onset (mean time to depression: 7.9 years). Becker *et al*[55] reported approximately twofold increased risk of developing depression in PD patients when compared to PD-free population.

Depression itself might be an independent risk factor for developing PD. This is because in patients with depression followed up for 10 years, 1.42% developed PD compared with 0.52% in the control group. In this study, patients with depression were 3.24 times more likely to develop PD compared with the those of the control group[56]. Moreover, patients with psychiatric illnesses exhibited 2.38-fold increased risk for developing PD compared with nonpsychiatric individuals. The highest risk for developing PD was observed in patients with schizophrenia[57]. The risk of the onset of major depression is influenced by genetic factors. This is due at least in part to the effect of genetic factors in modulating the individual's response to the depression-inducing effect of stressful life events[58]. Vanderheyden *et al*[37] found that 30% of PD patients had a history of mood disorder and 46% were prescribed an anxiolytic, an antidepressant, or an atypical neuroleptic, or a combination of these drugs. A study on first-degree relatives of patients with PD showed increased risk of depressive and anxiety disorders compared with first-degree relatives in the control group[59]. Puschmann *et al*[60] described a family with mild and slowly progressive L-dopa responsive autosomal dominant PD whose members also had depression. This suggests a common genetic vulnerability for mood disorders and PD.

The clinical manifestations of PD depression include apathy, psychomotor retardation, memory impairment, pessimism, irrationality, and suicidal ideation without suicidal behavior[61]. Depressed PD patients share many features that are present in depressed subjects without PD such as apathy, loss of initiative and decisiveness, insomnia, lack of energy and fatigue. The clinical spectrum of depression in PD patients differs in that features such as anhedonia, sadness, feelings of self-blame, feelings of guilt, sense of failure, self-destructive thoughts, suicide or suicidal ideation are much less common compared to patients with major depression not having PD. Concentration problems, however, are more common compared with depressed control subjects[62,63]. Suicidal ideation is not only a feature of major depression illness but also occurs in other neurological diseases, *e.g.*, multiple sclerosis, epilepsy, Huntington's disease, and PD. The most common risk factors being hopelessness, depression, and social isolation[64-66]. Major depression is a major risk factor for suicide and suicidal acts, which usually occur during major depressive episodes or mixed episodes[67]. Sokero *et al*[68] found that during the current major depressive episode, 58% of all patients had experienced suicidal ideation and 15% had attempted suicide most of whom (95%) had also had suicidal ideation. The severity of depression and current alcohol dependence or abuse was among factors that predicted suicide attempts. In their study, Subramaniam *et al*[69], reported that the prevalence of suicidal ideation, plan, and attempt to commit suicide among patients with lifetime major depressive illness was 43.6%, 13.7% and 12.3%, respectively. Inagaki *et al*[70] reported current suicidal ideation in 71.4% of patients with major depressive illness.

Suicide or death ideation are also common in depressed patients with PD. Kostić *et al*[71] found that in PD patients, followed for 8 years, the suicide-specific mortality was 5.3 times higher than expected. Current death and/or suicidal ideation were present in 22.7% of the patients. Major depression, psychosis, and hopelessness were associated with such ideation. Nazem *et al*[72] found that death ideation or suicide ideation were present in one-third of the sample, and 4% had a lifetime suicide attempt; increasing severity of depression, impulse control disorder, and psychosis were associated with either ideation. A lifetime prevalence of suicidal ideation in 11.6% of PD patients was also reported; the presence of depression and history of impulse-control disorder behaviors were important risk factors[73]. Other workers reported a prevalence of suicidal ideation in 14.4% of their sample but no attempted suicide; major depression being the

Table 2 Classification, mechanism of action and dosage range of antidepressants

Class	Mechanism of action	Generic name (trade name)	Dose range (mg/d)
Older antidepressants			
Mixed serotonin and norepinephrine reuptake inhibitors			
First-generation tricyclic antidepressants	Inhibit neuronal reuptake of norepinephrine and serotonin	Amitriptyline (elavil)	100-300
		Clomipramine (anafranil)	100-250
		Doxepin (adapin)	100-300
		Imipramine (tofranil)	50-300
		Trimipramine (surmontil)	100-300
		Protriptyline (vivactil)	75-200
		Lofepramine	15-60
Second-generation tricyclic antidepressants	Inhibit neuronal reuptake of norepinephrine and serotonin	Desipramine (norpramin)	100-300
		Nortriptyline (pamelor)	50-150
Tetracyclic antidepressants	Inhibit neuronal reuptake of norepinephrine and serotonin	Maprotiline (ludiomil)	100-200
		Amoxapine (asendin)	50-300
Heterocyclic agents Triazolopyridines	Mixed serotonin effects: Serotonin (5-HT2A) receptor blockade with serotonin reuptake inhibition	Trazodone (desyrel)	150-400
Monoamine oxidase inhibitors	Nonselective inhibitor of monoamine oxidase A and B	Phenelzine (nardil)	60-90
		Tranylcypromine (parnate)	20-60
		Selegiline (eldepryl)	5-10
Newer antidepressants			
Selective serotonin reuptake inhibitors	Selectively inhibit the reuptake of 5HT at the presynaptic neuronal membrane. Sertraline also markedly inhibits dopamine reuptake	Fluoxetine (prozac)	20-60
		Fluvoxamine (luvox)	100-300
		Paroxetine (paxil)	20-50
		Sertraline (zoloft)	50-200
		Citalopram (celexa)	20-40
		Escitalopram (lexapro)	5-20
Serotonin and noradrenaline reuptake Inhibitors	Potent inhibitors of 5HT and norepinephrine uptake; weak inhibitors of dopamine reuptake	Venlafaxine (effexor)	75-350
		Milnacipran (savella)	12.5-100
		Duloxetine (cymbalta)	60
Norepinephrine reuptake inhibitors	Noradrenaline reuptake inhibitor. Inhibits norepinephrine reuptake without inhibiting serotonin reuptake	Viloxazine	150-300
		Reboxetine (edronax)	4-8
		Atomoxetine (strattera)	40-80
Reversible inhibitors of monoamine oxidase A	Selective, reversible inhibitors of monoamine oxidase A: resulting in increased concentrations of NE, 5-HT, and dopamine in synapse	Moclobemide	300-600
		Brofaromine	75-150
5HT2 receptor antagonists/reuptake inhibitor serotonin modulators	Mixed serotonin effects. Inhibition of the reuptake of serotonin and selective postsynaptic 5-HT2A blockade	Nefazodone (serzone)	300-600
		Desvenlafaxine (pristiq)	50 mg once daily
		Ritanserin	5-10
5HT1a receptor agonists	Partial agonist of serotonin 5-HT1a	Gepirone, ipsapirone, tandospirone, felsinoxan	
α2-noradrenergic antagonists	Complex action on serotonin and noradrenaline *via* Serotonin (5-HT2A and 2C) receptor blockade and presynaptic α2-receptor blockade	Mirtazapine (remeron)	15-45
GABA-mimetics	GABAA and GABAB receptor agonists	Fengabine	900-1800
Dopamine reuptake inhibitors	Increases activity of norepinephrine and dopamine only; no significant effect on serotonin	Buproprion (wellbutrin)	200-450
Melatonin receptor agonists	Melatonin MT1 and MT2 receptor agonist and serotonin 5HT2C receptor antagonist	Agomelatine (valdoxan)	25-50
Herbal remedy: *Hypericum perforatum*/ St. John's wort	Unclear: inhibits the reuptake of several neurotransmitters, including 5HT, NE, dopamine, and γ-aminobutyric acid	*Hypericum perforatum*	300-900

Clomipramine, nefazodone and venlafaxine are potent non-selective serotonin reuptake inhibitors. Citalopram S-enantiomer, escitalopram, is the most active isomer and is a more potent and more selective serotonin reuptake inhibitor than citalopram. Extracts of *Hypericum perforatum* (St. John's Wort) are used in many countries to treat depressive disorders. GABA: Gamma aminobutyric acid; NE: Norepinephrine; 5HT: 5-hydroxytryptamine.

main predictor of suicidal ideation. Other factors were lower age of disease onset, panic disorder, and social anxiety disorder[74]. Interestingly, these figures are not higher than those reported in non-parkinsonian patients with major depression. It is noteworthy to mention that active suicidal ideation, lifetime suicidal attempts are associated with early-onset depression and young age[75]. The lower prevalence of suicidal ideation in depressed PD patients might be due to the fact that the disease occurs in old age.

FACTORS ASSOCIATED WITH DEPRESSION

Factors associated with depression include increased severity of motor disability, greater impairment in

activities of daily living[28,34,36,39,43,76], and longer disease durations[25,33,31,39,42,61]. Depression is more frequent in the young onset PD[34,43,45,76-78]. Similarly, those with subthreshold depression are younger (approximately 5 years) than non-depressed patients[27]. In contrast, Riedel *et al*[39] found that depression rates were already substantially elevated at early PD stages and that depression was not linked with age, age at onset of PD, or disease duration. In their study, van der Hoek[42] observed no difference in the prevalence of depression among the motor subtypes of PD. The authors, however, noted a trend towards higher prevalence of depression in the tremor dominant group of patients. In contrast, Dewey *et al*[79] found that patients with right-sided onset of tremor had a lower risk of depressive symptoms compared with other presentations. Meanwhile, the side and type of initial motor symptoms were not related to the risk of later cognitive impairment.

Gender imbalance is common in depression in non-PD subjects. McKercher *et al*[80] reported a prevalence of major depression of 5.5% for men and 11.6% for women. The prevalence of atypical depression is also higher in women than in men (24.6% *vs* 17.3%)[81]. Studies also suggested that depressive symptoms were more likely to occur in females than in males[42,82,83]. Other researchers observed no significant difference in the prevalence of depression between men and women with PD[42].

Stressful life events have been implicated in the onset of episodes of major depression[58]. Stressful life events are independent predictors of depressive symptoms in older adults[84] and in those who experience depression recurrence, exposure to acute life events predicts the evolution of residual symptoms to recurrence[85]. Depression in PD is associated with a history of anxiety disorder and memory problems[34] and with dementia[39]. Having a history of depression prior to onset of PD was predictive of depression with PD[45]. Significantly more serious depression also occurs in subjects with a history of depression before PD compared with those without such history[86]. Rod *et al*[46] suggested an important role for life events in onset of depression in patients with PD. The authors found that more than 50% of their sample experienced major life events since diagnosed with PD with major depression occurring in 9.9%. It was also noted that each additional event was associated with a 56% higher risk of depression. These observations stress the importance of social support in the management of PD patients with depression. Stressful life events are also important in non-PD depressed subjects.

Anxiety, memory problems, hallucinations, sleep disturbances are more common in depressed PD patients compared with PD patients without depression[34,76]. Apathy, a possible feature of depression, can exist independently and is often associated with cognitive impairment[87]. Depression in PD is often associated with anxiety[28,34,41,50] and both depression and anxiety might be early symptoms during the prodromal phase of PD[88]. Anxiety and apathy are significant comorbid conditions of moderate and severe depression[89]. Anxiety coexisted with depression in 8.6%[66] or 41% of the PD patients[50]. The figures are not higher than those encountered in non-PD patients. Thus, in patients with current episode of depression, generalized anxiety disorder and panic disorder comorbidities were associated with unipolar depression in 37.1% and 31.4% of patients, respectively[90]. In late-life depression in non-PD subjects, the prevalence rate of comorbid anxiety disorders was 38.6%[91]. Brown *et al*[44] suggested the presence of two clinical phenotypes of depression in depressed PD subjects, "anxious-depressed" and "depressed", with a large proportion of patients have relatively isolated anxiety. Depression and anxiety disorders were often unrecognized and untreated and the comorbidity greatly exacerbated PD symptoms[92]. It is likely that anxiety and depression in PD are due to different pathophysiological mechanisms[41].

COURSE OF DEPRESSION AND THE EFFECT OF DOPAMINERGIC DRUGS

Symptoms of depression are among the most frequent non-motor symptoms in the premotor phase of the disease. de la Riva *et al*[9] reported that newly diagnosed, untreated patients with PD experienced more depression, fatigue, apathy, and anxiety than healthy controls all time points; these remained relatively stable in early disease. Depression and other neuropsychiatric symptoms appear to be amenable to antiparkinsonian drug therapy, suggesting that they are related to or part of the disease process. In this context, Nègre-Pagès *et al*[41] found that patients with depressive symptoms received more frequently levodopa and less frequently a dopamine agonist. Similar observations were reported by Hanganu *et al*[93] who found that higher levodopa (L-dopa) dosages correlated with worse depressive symptoms. In contrast, there was no significant correlation between dopamine agonists and worsening of depressive symptoms. Spalletta *et al*[10] found significant improvement over time in the depression severity (also memory performance, and motor symptoms) in newly diagnosed patients with PD after 6-12 mo of antiparkinsonian therapy. Kulisevsky *et al*[94] found that among neuropsychiatric symptoms in PD, only depression was influenced by the type of medication, being less prevalent following treatment with dopaminergic receptor agonists. This suggested that depression in these patients is related to the dopaminergic deficit. Other neuropsychiatric symptoms such as impulse control disorders and excessive daytime sleepiness, however, are increasingly associated with the use of these drugs[9]. Even *et al*[95] identified three possible subtypes of comorbid depression associated with PD. The first category of patients is those who would develop depression even if they had no PD

(nonspecific-casual comorbid dPD). The second subtype includes patients who would be depressed because of another disabling medical illness (nonspecific-reactive comorbid dPD). The third group of patients are those in whom depression is directly related to the underlying pathophysiology of PD (specific comorbid dPD). This latter subtype might be partly responsive to dopamine replacement, suggesting a role for other neurotransmitter systems in its pathogenesis. There are data, however, that suggest a negative impact of dopaminergic pharmacotherapy on cognitive function in depressed PD patients in contrast to non-depressed patients who performed better while on dopaminergic medication[96].

Some dopaminergic medications appear to have antidepressant action unrelated to their influences on motor function. Pramipexole is a non-ergot dopamine receptor agonist which has been shown to be effective in reducing unified Parkinson's Disease Rating Scale (UPDRS) in early PD and as an "add on" therapy in advanced disease[97,98]. The UPDRS is used to assess both motor and nonmotor symptoms by listing numerous items to be scored by the examiner[5]. Studies suggest that pramipexole possesses a direct antidepressant effect. Thus, Barone *et al*[99] compared pramipexole to sertraline in a randomized trial in PD patients with major depression but no motor complications. They found that both agents decreased depression scores throughout treatment. The proportion of patients who recovered was significantly higher in the pramipexole compared to the sertraline group (60.6% *vs* 27.3%). In an open study of pramipexole as an add-on to L-dopa therapy or single administration, the scores of depressive symptoms, UPDR Scale III, and freezing of gait improved. No correlation was observed between depression scores and motor functions, suggesting an antidepressant effect for pramipexole[100]. Barone *et al*[101] conducted a 14-wk randomized trial comparing pramipexole with placebo in patients with mild-to-moderate PD without motor fluctuations who had depressive symptoms. The authors found that pramipexole improved depressive symptoms. Selegiline and rasagiline are irreversible selective inhibitors of the enzyme MAO-B that are effective as an initial monotherapy in early PD and as adjunct therapy to L-dopa in advanced PD[102-104]. Frampton *et al*[105] tested the efficacy of selegiline transdermal application in a randomized, double-blind, multicentre studies in adult outpatients with major depressive disorder. They found that short-term treatment with selegiline (6-12 mg/d) was superior to placebo on most measures of antidepressant activity. Long-term treatment with a fixed dose of 6 mg/d selegiline was also superior to placebo as maintenance therapy. In addition to improving motor performance, treatment with rasagiline (2 mg/d) in newly diagnosed PD patients who also have comorbid untreated depression, has been shown to improve depression symptoms. Rasagiline appears to have direct antidepressant action since it especially improved symptoms uninfluenced by motor function such as mood, guilt, psychic anxiety, and hypochondria[106].

NEURO-IMAGING STUDIES

It has been suggested that the development of depression in PD is likely to represent an advanced and widespread neurodegeneration of both serotonergic and dopaminergic neurons[76]. Imaging studies suggested that brain dopamine deficiency might have a role in depression in PD patients. Studies with 18F-fluorodopa-PET in *de novo* unmedicated PD patients showed that higher depression scores were associated with lower striatal 18F-fluorodopa uptake, suggesting that impaired striatal dopaminergic function is related to depressive symptoms in these subjects[107]. Other studies using [(123) I] FP-CIT single photon emission computed tomography (SPECT) tracer binding to the dopamine transporter (DAT) reported significant decrease in DAT availability in patients with PD. There was an association between dopamine loss in the caudate nucleus (lower DAT binding) and depressive symptoms[108,109]. In one study, reduced DAT binding was reported in the striatum in the majority of patients with major depression, indicating a role for dopamine hypofunction in this disorder. A more pronounced decrease in DAT binding occurred in PD patients (SPECT imaging using 99mTc-TRODAT-1)[110]. Bui *et al*[111] suggested that the decrease in striatal uptake in the context of a depressive episode might be reversible. The authors observed improved PD symptoms and increased DAT uptake {[(123) I] FP-CIT SPECT} in a depressed PD patient following treatment with electroconvulsive therapy. Ceravolo *et al*[112], however, reported increased bilateral striatal (123) I-FP-CIT uptake (DAT density) associated with the severity of both depressive and anxious symptoms in newly diagnosed PD patients. This was attributed to a lack of compensatory mechanisms and that it might have a pathogenic role in affective symptoms by reducing the dopaminergic tone in the synaptic cleft.

Not only dopaminergic pathways are affected in PD, but also cholinergic, serotonergic, and noradrenergic ones[113,114]. The neurobiology of depressive disorders involves alterations in serotonergic, dopaminergic and noradrenergic neurotransmission[115,116]. This forms the basis for the use of drugs such as tricyclic antidepressants (TCAs), serotonin reuptake inhibitors, noradrenaline reuptake inhibitors in the pharmacological management of depressive disorders[117,118]. Politis *et al*[119] used ^{11}C-DASB PET, a selective *in vivo* marker of 5-HT transporter binding to assess serotonergic function in patients with PD. They found relatively higher ^{11}C-DASB binding in raphe nuclei and limbic structures in those with highest scores for depression symptoms which might reflect reduced extracellular serotonin levels and decreased serotonergic neurotransmission. Beucke *et al*[120] suggested that un-medicated PD

patients have a low serotonergic activity which might be related to the dopamine deficit. Thus, auditory evoked potentials (indicator of central serotonergic function) were decreased in patients with PD compared with healthy subjects, but this difference was abolished following L-dopa treatment for 12 wk. The authors also noted a trend towards a correlation between auditory evoked potentials and DAT of the unmedicated patients [using (123) I-FP-CIT SPECT].

NEED FOR ANTIDEPRESSANT DRUG THERAPY

The presence of depression in PD subjects is under-recognized and consequently untreated. For instance, Althaus *et al*[121] reported a prevalence of depressive symptoms in 35.4% of their sample. Antidepressant drugs, however, were prescribed in 25.0% of patients suffering from moderate to severe depression. Moreover, depression was largely undertreated because a significant proportion of patients continued to experience depressive symptoms despite antidepressant drug therapy. In another study minor and major depression were found in 36.3% and 12.9% of the subjects, respectively. Only 8.6% of the minor depressed patients and 30.3% of the major depressed patients were prescribed antidepressant drugs[42]. Moreover, de la Riva *et al*[9] found that approximately two-thirds of patients with PD who screened positive for depression were not taking an antidepressant.

The development of depression in subjects with PD has a major impact on the quality of life and activities of daily living. The presence of neuropsychiatric symptoms such as depression, apathy, sleep disturbance and anxiety is associated with more severe parkinsonism compared with patients without these symptoms[29]. Depression also impacts on other cognitive functions. In one study, significant subjective memory complaints were reported by approximately 15% of PD patients and these worsen with increasing severity of depressive symptoms[32]. Subjects with left hemibody onset of motor symptoms and depression exhibited worse working memory, greater disability and lower quality of life compared with those without depression (and also relative to depressed subjects with left hemibody onset of motor symptoms)[122]. It has also been suggested that the presence of depressive symptoms (as well as dopaminergic drugs, disease severity and the occurrence of cognitive impairment) might underlie the onset of psychotic type symptoms in the early stages of PD[123]. Successful treatment of depression leads to important, sustained improvements in the quality of life and disability in PD patients[124].

ANTIDEPRESSANT DRUGS

The TCAs and the monoamine oxidase inhibitors (MAOIs) were the first classes of drugs employed in the pharmacological management of depressive symptoms. These agents work by increasing the synaptic concentration of the monoamine neurotransmitters; norepinephrine (NE), serotonin [(5-hydroxytryptamine, (5HT)] and dopamine. The MAOIs inhibit the enzymatic metabolism of neurotransmitters. The TCAs inhibit the neuronal uptake of NE and 5HT. The TCAs dominated the pharmacological management of depressive disorders for more than 30 years. With the advent of the new generations of antidepressants such as the selective serotonin reuptake inhibitors (SSRIs), the serotonin and noradrenaline reuptake inhibitors (SNRIs) and the noradrenaline reuptake inhibitors (NRIs), TCAs are no longer considered first-line treatments[125-127]. Table 2 lists different classes of antidepressant drugs and their mechanism of action.

ANTIDEPRESSANTS USED IN PD

TCAs

These include the tertiary-amine tricyclics, such as clomipramine, imipramine, amitriptyline, doxepin and trimipramine, and the secondary amines, such as desipramine, protriptyline and nortriptyline. These drugs owe their antidepressant properties to inhibition of the neuronal uptake of the monoamine neurotransmitters; norepinephrine, and serotonin (5-hydroxytryptamine, 5HT). Individual agents differ in their relative potency to inhibit the reuptake of either NE or 5HT. The tertiary tricyclics, amitriptyline, imipramine, and clomipramine are more potent in blocking the serotonin transporter while the secondary tricyclics are much more potent in blocking the norepinephrine transporter. These drugs as well as the tetracyclic compounds maprotiline and amoxapine have been approved for use in major depression with the exception of clomipramine, which in the United States is approved for use only in obsessive-compulsive disorder[128,129]. The TCAs dominated the pharmacological management of depressive disorders for more than 30 years. With the advent of the new generations of antidepressants such as the SSRIs, SNRIs and the NRIs, TCAs are no longer considered first-line treatments[125-127]. The TCAs have the capacity to block alpha1-adrenergic, H1 histaminergic and muscarinic receptors. The side effects include anticholinergic effects such as dry mouth, blurred vision, urinary retention and constipation. Sedative and cognitive effects should make their use in the elderly be largely avoided. Their slowed clearance in old age leads to drug accumulation and increased frequency and severity of side effects[13,130]. TCAs also cause weight gain, and sexual dysfunction[131]. TCAs cause cardiac conduction defects and arrhythmias by blocking fast inward Na^+ channels on myocardial cells. Blockade of postsynaptic peripheral α-adrenergic receptors contributes to the postural hypotension associated with TCA use[132]. The use of antidepressants in general and in particular TCAs is associated with tachycardia[133].

TRICYCLIC ANTIDEPRESSANT DRUGS IN PARKINSON'S DISEASE

TCAs were the first class of antidepressant medications to be used for the treatment of depression in patients with PD. These agents were found more effective than placebo and even better than some of the SSRIs. Thus, Andersen *et al*[134] treated patients with nortriptyline for 16 wk and observed larger improvement compared with placebo. A meta-analysis by Frisina *et al*[135] of 24 placebo-controlled trials found that TCAs had a greater antidepressant effect relative to SSRIs and the mono-amine-oxidase inhibitor, selegiline. Side effect profile was, however, in favor of SSRIs. A more recent meta-analysis by Liu *et al*[136] concluded that TCAs might be the best choice when starting antidepressant treatment in patients of PD. In a study comparing amitriptyline and fluoxetine, Serrano-Dueñas[137] found that amitriptyline (approximately 35 mg/d) was better than fluoxetine at controlling the depression. Side effects that occurred in 15% of the patients on amitriptyline treatment, however, led these patients to abandon the drug. Antonini *et al*[138] compared low-dose amitriptyline (25 mg) to the SSRI sertraline (50 mg) on depression and quality of life in a prospective single-blind randomized study. Drugs were administered for 3 mo. Responder and completion rates were 83.3% and 75% for sertraline and 72.7% and 73% for amitriptyline, respectively. Sertraline and not amitriptyline treatment had a significant benefit on quality of life. (Whether the dopamine reuptake inhibition by sertraline is involved is an intriguing possibility!).

The short-term efficacy of desipramine was compared to that of citalopram, a SSRI in a double-blind, randomized, placebo-controlled study. The authors found that desipramine induced a more rapid improvement (after 14 d) in depression score than did an SSRI and placebo. After 30 d both drugs significantly improved depression. Thus a predominantly noradrenergic reuptake inhibitor TCA was faster than an SSRI in controlling depression in PD[139]. Moreover, nortriptyline, another TCA which mainly inhibits noradrenaline reuptake was found superior to placebo in decreasing depression scores. In this randomized, placebo controlled trial, the SSRI paroxetine controlled release (CR), however, was not efficacious. Response rates for nortriptyline, paroxetine CR, and placebo were 53%, 11%, and 24%, respectively[140].

TCAs possess antihistaminic effects which might be of benefit in those suffering from insomnia. One randomized pilot study assessed non-pharmacologic treatment or doxepin, compared to placebo in PD patients with insomnia. Compared to placebo, doxepin improved insomnia, sleep quality, clinical global impression of change. The drug also reduced fatigue severity and improved cognitive scores[141]. Clomipramine, a drug with prominent 5HT reuptake inhibitory action was reported to improve delusions and hallucinations in a parkinsonian patient with psychosis and comorbid depression[142].

Recently, a study by Paumier *et al*[143] in early PD patients showed that TCAs resulted in delaying the time to initiation of dopaminergic therapy compared with patients not on antidepressants. There were no changes in Unified PD Rating Scale (UPDRS) scores. The effect of TCAs thus could not be attributed to symptomatic effects.

Table 3 lists selected studies on the effect of TCAs on depressive symptoms in subjects with PD.

SSRIs

These agents are considered first line treatments of depression due to their more safety profile compared to the TCAs[144]. The SSRIs differ in their potency and selectivity in inhibiting serotonin reuptake and in their pharmacokinetics. The prototype SSRIs is fluoxetine which acts by blocking the reuptake of 5HT at the presynaptic neuronal membrane, thereby increasing its concentration in the synaptic cleft[145]. Fluoxetine has longer elimination half-life of 1-3 d after acute administration, while its active metabolite norfluoxetine has a half life of 7-15 d[128]. Its abrupt cessation is not likely to cause discontinuation reactions[146].

Fluvoxamine and paroxetine are other potent SSRIs with an elimination half-life of 15 and 21 h, respectively[144,147]. The abrupt discontinuation of paroxetine results in withdrawal symptoms, including nightmares, tremor, dizziness, insomnia, myalgias, and a "flu-like" syndrome[148]. It is thus advisable to taper the medication over several days, particularly in patients receiving more than 20 mg per day[145]. The drug is a first-line treatment option for major depressive disorder, dysthymia or minor depression[149].

The inability of citalopram to cause significant inhibition of hepatic enzymes made the agent an attractive agent for the treatment of depression, especially among the elderly and patients with comorbid illness requiring concomitant medicines[150,151]. Escitalopram is the pure S-enantiomer of the racemic compound citalopram and the pharmacologically active enantiomer of the racemate which have a more potent antidepressant than that of citalopram. Escitalopram is approximately 30-fold more potent than R-citalopram[152,153].

The SSRIs affect the reuptake of other neurotr-ansmitters. Thus, fluoxetine also acutely increases the extracellular concentrations of NE and dopamine (as well as 5HT) in prefrontal cortex[154] and unlike the other SSRIs possesses moderate affinity for the serotonin 2C receptor[152]. Paroxetine and sertraline possess moderate affinity for the human NE transporter and dopamine transporter, respectively[152]. Sertraline has been shown to increase extracellular levels of dopamine in the nucleus accumbens and striatum[155] which might have important clinical consequences. Paroxetine displays affinity for the muscarinic cholinergic receptor and causes a higher rate of anticholinergic effects, such as dry mouth, constipation, and cognitive

Table 3 Prevalence of depressive symptoms in subjects with Parkinson's disease in different studies

Stage of PD/type of patients	No. of patients/ sample size	Prevalence of depression/ depressive symptoms	Prevalence of other neuropsychatric symptoms	Ref.
Outpatients, non-fluctuating (21 de novo, 69 treated with levodopa or dopamine agonists)	90	Major depression in 21.1% (*vs* in 3.3% controls)	Panic disorders in 30% (*vs* 5.5% in controls) Dystimia in 18.8% (*vs* 4.4% in controls)	[26]
Outpatients with established PD	100	Major depression in 35%		[35]
Patients with PD presenting with non-motor symptoms. Retrospective study of pathologically-proven PD	91	Depression in 2.5%	Anxiety in 3.9%	[33]
Outpatients with established PD	50	Major depression in 42% (*vs* 10% of geriatric patients)		[28]
Nondemented patients with moderate to severe PD	111	Depression in 26.1% Subthreshold depression in 28.8%		[27]
Early untreated PD	175	Depression in 37%	Apathy in 27% Sleep disturbance in 18% Anxiety in 17%	[29]
New-onset PD patients	685	Depression in 72% (developed depression within ten years of symptomatic PD onset)		[36]
Outpatients with established PD	1086	Major depression in 15.6%		[37]
Outpatients with established PD	1449	Depression in 25%	Anxiety in 20% Dementia in 29% Psychotic syndromes in 12.7% Sleep disturbances in 49%	[38]
Outpatients with established PD	1449	Depression in 33.6%		[39]
Outpatients with established PD	150	Depression in 43% Depression without apathy in 13%	Apathy only in in 17% Apathy + depression in 43%	[40]
Non-demented PD subjects	105	38% borderline depression Major depression in 4.8%		[30]
Non-demented PD subjects	450	Depressive symptoms in 40% (*vs* 10% of controls)	Probable anxious signs in 51% (*vs* 29% of controls)	[41]
Patients with established PD	256	Minor depression in 36.3% Major depression in 12.9%		[42]
Patients with established PD	360	Depression in 41.3%	Only apathy in 23% Apathy + depression in 36.9%	[43]
Patients with established PD	202	Depression in 37.3%	Anxiety in 31.3%, Dementia in 25.3% Excessive daytime sleepiness in 59.4%	[31]
Patients with established PD	513	Depression in 8.6%	Anxiety alone in 22.0% Anxiety + depressive symptoms in 8.6%	[44]
Outpatients with established PD	158	Depression in 11% to 57% (depending on the definition of depression)		[45]
Outpatients with established PD	639	Depression in 66%		[34]
New-onset PD patients	221	Major depression in 9.9% (developed depression over 3-4 yr)		[46]
Outpatients with established PD	1449	Depression in 18.8%	Dementia in 13.9% had Dementia + depression in 14.3%	[47]
Non-demented PD subjects	95	Depression in 28%		[48]
Early stage PD	36	Depression in 36.1%	Anxiety in 27% Obsessive-compulsive symptoms in 52.8% Somatization in 66.7%	[49]
Outpatients with established PD	117	Depression in 56%	Anxiety in 55%	[50]
Patients with established PD (ambulatory and home residents)	886	Depression in 24.4%	28.4% dementia (20.6 % of ambulatory and 85.7 % of home residents)	[51]
PD patients with mild cognitive impairment	104	Depression in 40.4% (*vs* 16.6% in controls)	Subjective memory complaints 16.3% (*vs* 7.7% of controls)	[32]
Non-demented PD subjects	115	Major depression in 28.7% Subthreshold depression in 26.10%		[52]

PD: Parkinson's disease.

disruption, compared with other SSRIs. These effects may be particularly difficult to tolerate for elderly or concomitantly medically ill patients[156]. There are also data to suggest that long-term treatment with paroxetine increases GABA, glutamate, dopamine and noradrenaline levels in the brain[157].

The most common side effects associated with SSRIs include initial nervousness or agitation, anxiety, headache, insomnia, dizziness, dry mouth, gastrointestinal symptoms (nausea, diarrhea, constipation) and sexual dysfunction[144,158]. The use of SSRIs is likely to increase the risk of upper GI bleeding, and this effect is potentiated when these drugs are used in combination with nonsteroidal anti-inflammatory drugs or low-dose aspirin. Other antidepressant drugs did not appear to have an effect on the risk of upper GI bleeding[159]. Other studies reported increased risk of upper gastrointestinal bleeding after short-term SSRI use (7-28 d) intake in male but not female patients[160]. Prior use of SSRIs has also been implicated in increased stroke severity and mortality in patients with hemorrhagic stroke. This, however, was not seen in in SSRI users with ischemic stroke[161]. SSRI/SNRI antidepressants and in particular sertraline and escitalopram have been shown to increase the risk of hyponatraemia, especially in depressed patients aged > 63 years[162]. Recent evidence also implicates SSRIs with decreased bone mineral density and increased risk of hip fracture which appear to decline after discontinuation of these agents[163,164]. SSRIs are associated with a modest but statistically significant increase in the QTc interval with citalopram being associated with more QTc prolongation than most other SSRIs. The increase in QTc by TCAs is however, significantly greater than that of SSRIs[165].

SSRIs in PD

Case reports have associated some of the SSRIs with extrapyramidal side effects. Leo[166] in a review of case reports and case series of movement disorders attributed to SSRIs found that among the 71 cases reported in the literature, the most common side effect was akathisia, dystonia, parkinsonism, and tardive dyskinesia-like states, with a frequency of 45.1%, 292.%, 14.1% and 11.3% respectively. Fluoxetine was implicated in 74.6% of cases of SSRI-induced extrapyramidal symptoms. Other concomitant drugs that can contribute to the development of extrapyramidal symptoms were likely in 57.7% of reports. Caley *et al*[167] in a retrospective study of medical records of 23 outpatients with Parkinson's disease who were receiving or had received fluoxetine up to 40 mg/d, found that 20/23 of patients experienced no worsening of their symptoms.

Studies in PD patients with depression, however, have shown treatment with SSRIs to be mostly safe and efficacious. A study of 66 patients with non-fluctuating, depressed patients with PD found a significant improvement in depressive symptoms with citalopram, fluoxetine, fluvoxamine, and sertraline 6 months after starting treatment. There was no significant change in UPDRS scores. The study, however, comprised a small number of patients (15-16) in each drug subgroup[168]. Rampello *et al*[169] treated depressed (n = 16) and nondepressed (n = 14) PD patients with citalopram (up to 20 mg/d) and observed improved depressive symptoms in 15/16 patients with depression. Moreover, citalopram did not worsen motor performance and on the contrary improved bradykinesia and finger taps in subjects with and without depression on levodopa.

Studies have also indicated an ability of paroxetine to improve depression in depressed PD patients. Tesei *et al*[170] administered paroxetine (10-20 mg/d) to 65 outpatients with PD and depression and found improved depression scores in 52 patients after approximately 3 mo. Adverse reactions which occurred in 13 patients led them to stop treatment. There were also increased "off" time and tremor in 2 patients that reversed after stopping paroxetine. In another study by Ceravolo *et al*[171] 6 mo therapy of paroxetine (20 mg/d) improved depression without an effect on motor function (UPDRS scores). Reversible worsening of tremor was observed in one patient. Chung *et al*[172] who examined the motor effects of 2 wk of paroxetine and placebo on responses to 2-h levodopa infusions, found no effect for the drug on tapping scores or dyskinesia. Paroxetine increased baseline walking speed (prior to infusion) but with increased subjective perception of worsened balance. In a randomized, double-blind, placebo-controlled trial, both paroxetine and venlafaxine XR were efficacious in improving depression without effects on motor function. The mean 12-wk reductions in depression score were 6.2 points for paroxetine group and 4.2 points for venlafaxine XR[173]. A randomized, controlled trial of paroxetine CR, nortriptyline, and placebo in 52 patients with PD and depression, however, failed to demonstrate a benefit from paroxetine[142].

In their study, Kostić *et al*[174] administered fluoxetine at daily dose of 20 mg to patients with PD and mild depression. The authors reported significant improvement in depression and UPDRS scores. These correlated with steady state plasma concentrations of fluoxetine and its metabolite norfluoxetine. In an open label trial of 10 patients with PD and major depression, citalopram improved depression, anxiety and functional impairment significantly[175]. In another open-label study of 14 PD patients with major depression, escitalopram treatment was well tolerated with a significant decrease in depressive symptoms, although response rate was only 21%[176]. In a double-blind, randomized, placebo-controlled study of PD patients with major depression, citalopram (and desipramine) produced significant improvements in the depression score after 30 d[139].

Sertraline was found effective in relieving depression in patients with PD without significant effect on motor performance[177]. Sertraline was of comparable efficacy to amitriptyline in decreasing depression scores in PD patients with depression. In this prospective single-blind randomized study, the responder rates were 83.3% and 72.7% for sertraline and amitriptyline, respectively. Sertraline but not amitriptyline, improved quality of life (mobility, activities of daily living)[138]. Kulisevsky *et al*[178] in a large sample of 374 depressed PD patients of whom 310 completed the study found that treatment with sertraline decreased depressive scores and also improved UPDRS scores. There was

worsening of tremor in some patients. Sertraline in both the usual formulation and in the liquid oral concentrate was found efficacious in deceasing depressive scores. Quality of life improved with sertraline (clinical global impression-severity of illness scale and clinical global impression-global improvement scale scores) after 6 mo of treatment. This occurred without change in UPPDR Scale motor scores[179].

OTHER ANTIDEPRESSANTS

Trazodone and nefazodone

Trazodone and nefazodone are chemically related with complex serotonergic actions. These drugs antagonize 5HT2A and 2C postsynaptic receptors. Blockade of these receptors leads to facilitated neurotransmission through $5HT_{1A}$ receptors, which reduces anxiety levels. In addition both drugs inhibit the reuptake of 5HT to some extent. They thus possess antidepressant, and also some anxiolytic and hypnotic activity, and have favorable sleep architecture profile[180]. Nefazodone has weak affinity for cholinergic and noradrenaline α_1- adrenergic receptors and, therefore, is associated with less sedation and orthostatic hypotension than trazodone. The drug has favorable effect on sleep pattern in contrast to fluoxetine which has been shown to not improve sleep in depressed patients[181,182]. Thus, nefazodone would be suitable for depressed patients with prominent features of anxiety and agitation and loss of sleep[105]. Sedation, dry mouth, nausea, and dizziness are the more common adverse effects of nefazodone[183]. In the treatment of major depression, these agents do not differ from the SSRIs with respect to overall efficacy and tolerability[184].

In PD patients with depression, Avila *et al*[185] provided data suggestive of motor improvement (UPDRS score) after nefazodone, but not after fluoxetine treatment. Meanwhile, both drugs were equally effective as antidepressants. In another study, by Werneck *et al*[186] trazodone improved depression and motor function improved in the depressed patients treated with the drug.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant. The drug increases noradrenergic and 5HT transmission *via* presynaptic α_2-antagonism. Mirtazapine increases the release of NE from central noradrenergic neurons by blocking the presynaptic inhibitory α_2-autoreceptors. It blocks the inhibitory α_2 heteroreceptors on serotonergic neurons, resulting in increased release of serotonin. Mirtazapine also blocks histamine H1 receptors, thus causing sedation, but has little effect on acetylcholine, dopamine or noradrenaline α_1 receptors. The most common side effects are dry mouth, sedation, increased appetite, and weight gain[144,187]. Mirtazapine has a faster onset of action compared with to SSRIs[188,189]. Case reports suggested a positive effect of mirtazapine on auditory[190] and visual[191] hallucinations in patients with PD and persistent psychosis without worsening motor symptoms. This antipsychotic effect of mirtazapine was attributed to 5HT-2A and/or 5HT-2C antagonism leading to dopamine release[190].

Venlafaxine

Venlafaxine is a serotonin and SNRI[144]. Venlafaxine has a rapid onset of clinical action (one week or two). In the treatment of in-patients with major depression venlafaxine was superior to fluoxetine[192]. It is used to treat melancholia (endogenous depression) and treatment-refractory depression[128]. Remission rates were significantly higher with venlafaxine than with an SSRI[193]. A single-blind study in elderly patients suffering from resistant major depression, found venlafaxine to be significantly superior to paroxetine in improving depression[194]. Adverse effects of the drug include nausea, somnolence, insomnia, and dizziness, constipation, sweating, nervousness, and abnormal ejaculation, cardiac conduction changes[128]. In non-fluctuating PD patients with depression, venlafaxine treatment for 8 wk improved depression without changes in UPDRS scores[195]. In a randomized, double-blind, placebo-controlled trial in depressed PD patients, venlafaxine extended release was effective in improving depression. The mean 12-wk reductions in depression score were 6.2 points for paroxetine group and 4.2 points for venlafaxine extended release[173].

Atomoxetine

In subjects with PD and depression, treatment with the SNRI atomoxetine was not found efficacious in relieving depressive symptoms. Global cognitive performance and daytime sleepiness, however, significantly improved[196].

Duloxetine

Duloxetine is a serotonin and noradrenaline reuptake inhibitor. In an open-label study in PD patients with major depression, duloxetine 60 mg once daily significantly improved depression scores and activities of daily living without worsening rigidity or tremor[197].

Table 4 lists selected studies on the effect of SSRIs and other antidepressant drugs on depressive symptoms in subjects with PD.

NON-PHARMACOLOGICAL TREATMENT MODALITIES

Neurostimulation

Electrical neurostimulation techniques include deep brain stimulation (DBS) of subthalamic motor nuclei or globus pallidus internus, transcranial magnetic stimulation (TMS), and electroconvulsive therapy.

Table 4 Studies on the effect of antidepressant drugs on depressive symptoms in Parkinson's disease subjects with depression

Drug	Study design	Sample size	Study objectives	Outcomes	Adverse effects	Ref.
Fluoxetine		23	Effects of fluoxetine (up to 40 mg/d) on motor performance	20/23 patients experienced no worsening of parkinsonism		[167]
Fluoxetine, fluvoxamine, citalopram, and sertraline	Open-label prospective study	62 depressed patients with PD (without dementia or motor fluctuation) (15 patients received citalopram, 16 fluoxetine, 16 fluvoxamine, and 15 sertraline)	Effects of SSRIs on motor performance and depressive symptoms	↓↑ UPDRS scores Significant improvements in depression with all SSRIs		[168]
Fluoxetine/ amitriptyline	Randomized study	77 patients with PD (37 received fluoxetine and 40 received amitriptyline)	Comparing fluoxetine (20-40 mg/d) and amitriptyline (25-75 mg/d) at low doses on depressive symptoms	Amitriptyline better controlled depression at 3, 6, 9 and 12 mo, respectively	15% abandoned amitriptyline because of side effects	[137]
Fluoxetine	Prospective, controlled, open-label study	18 patients with PD and mild depression without dementia	Influence of fluoxetine (20 mg/d) on motor functions	Significant improvements in scores of depression and Parkinson's disability		[174]
Paroxetine			To assess the tolerability of paroxetine (20 mg once per day)	Improved depression UPDRS scores ↓↑	Reversible worsening of tremor in one patient	[171]
Paroxetine		65 outpatients with PD and depression	To assess the tolerability of paroxetine (10-20 mg once per day)	Improved depression	20% stopped paroxetine because of adverse reactions Increased "off" time and tremor in 2 patients (reversible)	[170]
Paroxetine CR/ nortriptyline	Randomized, placebo controlled trial	52 patients with PD and depression	To evaluate the efficacy of paroxetine CR and nortriptyline in treating depression	Nortriptyline was superior to placebo for the change in depressive scores Paroxetine CR was not		[140]
Paroxetine/ venlafaxine	Randomized, double-blind, placebo-controlled trial	115 subjects with PD	To compare efficacy and safety paroxetine and venlafaxine extended release in treating depression in PD	Both paroxetine and venlafaxine XR significantly improved depression UPDRS scores ↓↑		[173]
Citalopram		46 non-demented patients with PD. 18 depressed and 28 non-depressed	Effect of citalopram on motor and nonmotor symptoms of depressed and nondepressed patients with IPD	Improvement in mood in 15/16 patients Motor performance ↓↑ Improved bradykinesia and finger taps in patients with and without depression		[169]
Citalopram	Prospective, open label trial	10 patients with PD and major depression, without dementia	Effects of citalopram on depressive symptoms	Significant improvement in depression and in anxiety symptoms and functional impairment		[175]
Escitalopram	Open-label study	14 Parkinson's disease patients with major depression	Effects of escitalopram on depressive symptoms	↓ in depressive symptomatology score (response and remission rates were only 21% and 14%)		[176]
Sertraline	Open-label pilot study	15 patients with PD and depression	To evaluate the safety and efficacy of sertraline to treat depression in PD	Significant improvement in depression UPDRS scores ↓↑	Side effects in 1/3 2 patients discontinued sertraline	[177]
Sertraline		54 PD patients with depressive disorders	Comparing efficacy of sertraline in the usual formulation and in the liquid oral concentrate	Improved depression on both formulations Improved clinical global impression-severity of illness scale		[179]
Sertraline		374 PD patients with depressive symptoms	Long-term effects of sertraline on motor status	Improved UPDRS ↓ Anxiety ↓ Depression	8% discontinued medication for adverse events (gastrointestinal) Worsening of tremor in some patients	[178]

Sertraline/ amitriptyline	Prospective single-blind randomized study	31 patients with PD and depression	Assessment of the effect of sertraline (50 mg) or low-dose amitriptyline (25 mg) on depression and quality of life	↓ Depression by both drugs Sertraline improved quality of life ↓↑ UPDRS scores		[138]
Sertraline/ pramipexole	Randomized trial	67 outpatients with PD and major depression but no motor fluctuations and/or dyskinesia	To compare pramipexole with sertraline	Both sertraline and pramipexole improved depression Pramipexole caused more recovery compared to sertraline (60.6% *vs* 27.3%) Pramipexole improved UPDRS motor subscore	14.7% withdrew from the sertraline group	[99]
Nefazodone/ fluoxetine	A pilot randomized trial	Depressed patients with PD	To assess the effect of nefazodone on extrapyramidal symptoms in depressed PD patients	Nefazodone significantly improved UPDRS score Both nefazodone and fluoxetine were equally effective in treating depression		[185]
Trazodone	Randomized trial	20 PD patients with and without depression	To test the ability of trazodone to improve depression and motor function	Significantly improved depression Improves motor function in depressed patients		[186]
Venlafaxine	Prospective study	14 non-fluctuating PD patients with depression	To investigate the therapeutic efficacy of venlafaxine	Improved depression scores UPDRS scores ↓↑		[195]
Atomoxetine, a SNRI	Randomized placebo- controlled study	55 subjects with PD depression atomoxetine or placebo	To assess efficacy of atomoxetine (80 mg/d) in treating depression	Failed to improved depression Improved global cognition Improved daytime sleepiness		[196]
Duloxetine	Non-comparative, open-label, multi-center study	151 patients	To evaluate the tolerability, safety, and efficacy of duloxetine 60 mg once daily in PD patients with major depressive disorder	Improved depressive scores Improved activities of daily living Tremor ↓↑ Rigidity ↓↑	8.6% discontinued the study due to side effects	[197]

PD: Parkinson's disease; SNRI: Selective norepinephrine reuptake inhibitor; UPDRS: Unified Parkinson's disease Rating Scale.

DBS surgery

This involves inserting microelectrodes into the basal ganglia nuclei, *e.g.*, subthalamic nucleus or globus pallidus internus. In advanced stage PD, deep brain stimulation of subthalamic nucleus improves motor function, motor fluctuations, dyskinesia, activities of daily living, quality of life and allows dopaminergic treatment reduction or withdrawal in a subset of patients[198-206]. Improvement in anxiety, depression, and fatigue has also been reported following subthalamic stimulation[199,200,202,206-208]. In addition, patients with severe PD subjected to bilateral subthalamic nucleus DBS were reported to have had significantly longer survival[209]. The effect of subthalamic DBS on depression, however, might not be maintained. In one study, motor UPDRS-III scores decreased within 18 mo postoperatively compared with preoperative and the medication control group. Self-Rating Depression Scale and Hamilton Rating Scale for Depression decreased within 6 and 3 mo postoperatively, respectively[202]. Cognitive deterioration[203,207,210], decline in verbal fluency and in abstract reasoning, episodic memory and executive function[211], depression[202,205,212,213], apathy[212], worsening of apathy[214] as well as the unmasking of previous psychiatric problems[215] might complicate the procedure. The increase in affective-cognitive symptoms of depression after DBS might reduce the procedure-induced motor improvement[213]. Suicide has also been reported among patients undergoing subthalamic nucleus DBS, despite clear motor improvements[213,216]. Other studies, however, reported no increased risk for suicide ideation and behaviors among PD patients subjected to subthalamic nucleus or globus pallidus interna DBS surgery[217]. Operative complications include infection, intracerebral hematoma, chronic subdural hematoma, electrode fracture, and incorrect lead placement, phlebitis, and pulmonary embolism[204,205,218].

TMS

Brain stimulation with TMS is a noninvasive approach of electrically stimulating neurons in the human cerebral cortex that is capable of modifying neuronal activity both locally and at distant sites[219]. The technique of TMS involves the passage of an electrical current through a copper-wire coil placed on the scalp. A brief, rapid time changing magnetic field is created at the level of the

coil which then induces a small electrical current in the underlying brain. Depolarization of neuronal membranes and generation of action potentials follows. In repetitive TMS (rTMS), repeated electrical pulses are generated in the cortex[220,221]. Repetitive TMS of the left dorsolateral prefrontal cortex was approved for the treatment of major depression in United States in 2008[222]. The technique appears to be without side effects[222,223]. Maruo *et al*[223] observed that three consecutive days of HF-rTMS over the M1 foot area in patients with PD failed to improve depression and apathy scales, despite significant improvement in UPDRS-III compared to sham stimulation.

Electroconvulsive therapy

In PD patients with refractory psychiatric symptoms, electroconvulsive therapy (ECT) led to improvement in symptoms of psychosis and motor symptoms with no adverse effects[224]. There are case reports that ECT was successful in the treatment of severe anxiety[225], and obsessive compulsive disorder[226] in PD, depression and parkinsonism in drug-induced parkinsonism[227]. Usui *et al*[228] reported improvement of psychosis and severity of PD in eight patients with levodopa or dopamine agonist-induced psychosis. The technique has also been used to treat depression in patients implanted with DBS. Chou *et al*[229] found that ECT dramatically improved major depression with psychotic features that occurred after bilateral subthalamic nucleus DBS surgery. Nasr *et al*[230] reported the treatment of severe depression with psychotic features and the decline in physical and mental states using ECT in a patient implanted with DBS. A randomized, double-blind trial of transcranial electrostimulation in early PD, however, found no significant effect on anxiety or depression and also on motor symptoms[231].

Neurosurgical ablation techniques

Surgery, *e.g.*, pallidotomy, subthalamotomy are sometimes used to alleviate motor symptoms in advanced PD patients refractory to medical treatment[232]. Surgery still might be resorted to in some instances where DBS is contraindicated or following complications necessitating removal of the implanted device[233]. In one study, lasting improvement in depression and apathy and no cognitive deterioration were reported in patients with advanced PD subjected to simultaneous bilateral subthalamotomies[234]. In another study, advanced PD subjects with depressed mood subjected to left-posteroventral pallidotomy performed worse on measures of verbal list learning and story recall when compared to non-depressed subjects or right-posteroventral pallidotomy subjects with depressed mood[235].

Cognitive behavior therapy

This psychotherapeutic treatment option improves comorbid depression and anxiety and the quality of life in PD patients[236,237]. In one study, patients on cognitive behavior therapy reported greater reductions in depression scores, anxiety, and improved quality of life compared with the clinical monitoring group[238]. Cognitive behavior therapy delivered *via* telephone to persons with PD also proved useful in improving psychiatric symptoms[239].

Insight from animal studies

The use of animal models of PD has greatly enabled our understanding of the pathogenetic mechanisms of depression in PD and also helped to identify potential therapeutic targets. Many studies employed the neurotoxin 6-hydroxydopamine (6-OHDA) which when injected into the striatum of rats induces marked depletion of dopamine, serotonin and also noradrenaline in the striatum[240]. Using this model, Tadaiesky *et al*[241] demonstrated that anxiogenic- and depressive-like behaviors occur early in the course of experimental parkinsonism analogous to that in early phases of human PD. This occurred along with alterations of dopamine, serotonin and noradrenaline in the striatum. Mild anxiogenic effects were also reported in 6-OHDA-lesioned rats. These effects were not amenable to treatment with L-dopa[242]. Branchi *et al*[243] found depressive-like behavior but reduced anxiety and a marked change in social behavior and no learning or memory difficulties in 6-OHDA-lesioned rats. Courtière *et al*[244] using the reaction time task test provided data that 6-OHDA lesioned rats had cognitive impairment similar to PD patients. These studies indicated that behavioral changes also occur in early phases of experimental PD. Studies in rodents also allowed the evaluation of such techniques as, TMS, rTMS and DBS. Thus high-frequency electrical stimulation of the subthalamic nucleus in rats was shown to increase striatal dopamine efflux, thereby indicating that the benefit from this technique is probably due to enhanced dopamine release within the basal ganglia[245]. Extracellular levels of 5HT in both striatum and medial prefrontal cortex also decreased following high-frequency electrical stimulation of the subthalamic nucleus even in dopamine-denervated rats. Changes in 5HT neurotransmission might therefore account for the depression seen in some patients following DBS of the subthalamic nucleus[246]. Ghiglieri *et al*[247] found that rTMS increases striatal excitability and rescues corticostriatal long-term depression in experimental parkinsonism in rats.

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