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Depression in Parkinson's Disease:

Pharmacological Characteristics and Treatment

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Summary

Parkinson's disease (PD) is a common neurological illness and various degrees of depression frequently complicate its course. Risk factors for developing depression with PD include right-sided hemiparkinsonism, akinesia, increased severity of disability, anxiety and psychosis. Onset of parkinsonism at a younger age, female gender and the use of levodopa are arguable risk factors. Depression may be difficult to diagnose in patients with PD because the signs of the 2 disorders overlap. In addition, patients with atypical PD more commonly have depression than patients with classical PD presentations.

Antidepressant response to antiparkinsonian treatment has been limited. Enhancement of catecholamine levels in the CNS by selegiline (deprenyl), a monoamine oxidase (MAO) type B inhibitor, has shown potential antidepressant as well as neuroprotective effects. Other MAO inhibitors have shown antidepressant efficacy in animal models but have not been well tolerated by patients with PD. A catechol-*O*-methyltransferase (COMT) inhibitor combined with an MAO inhibitor might synergistically maximise the levels of catecholamines in the CNS.

Antidepressant medications used in patients without PD include tricyclic antidepressants (TCAs) and selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs), but only TCAs have been carefully studied for their antidepressant effects in PD. Electroconvulsive therapy has proven efficacy as antidepressant therapy in patients with PD, and transcranial magnetic stimulation has provided temporary relief of depression under experimental conditions.

Adverse effects of polypharmacy in the attempted treatment of depression in patients with PD are common in the elderly. A 'serotonin syndrome' has occurred frequently enough to preclude the coadministration of selegiline with SSRIs or TCAs, and multiple interactions between antiparkinsonian and antidepressant medications further complicate treatment strategies in patients with PD.

An algorithmic approach to the pharmacological treatment of depression is described in this article.

Parkinson's disease (PD) is a common neurological illness with an overall prevalence of approximately 100 per 100 000 people. The prevalence increases with age from 2.3 per 100 000 people for those aged <50 years to 1100 per 100 000 for those aged >80 years.[1] PD is the most commonly encountered extrapyramidal movement disorder. The primary manifestations of PD result from the idiopathic degeneration of dopaminergic neurons in the substantia nigra and pars compacta and include resting tremor, bradykinesia, loss of postural reflexes and rigidity. The course of this illness is a long one. Two-thirds of patients with PD are disabled 5 years after the onset of illness.[2]

1. Depression and Parkinson's Disease (PD)

Depression of various degrees of severity commonly complicates the course of PD. Most often, depression is not a reaction to physical disability, but is an integral expression of brain dysfunction. Depression accounts for the majority of psychiatric referrals of patients with PD.[3,4] Although a community-based study found that only 7.7% of patients with PD meet the criteria of the Diagnostic and Statistical Manual of Mental Disorders, revised third edition (DSM-III-R)[5] for major depression, approximately 46% were found to have mildly depressive symptoms.[6] The estimated rate of clinically important depression in patients with PD (37%) is more than twice that seen in medically ill patients (18%).[7]

Depression may be a prodromal symptom of PD;[8] in one study of depressed patients with PD, mood changes were found to predate the onset of the first motor sign.[9]

1.1 Risk Factors

Possible risk factors for developing depression with PD include young age, younger age at onset of PD, female gender, right-sided hemiparkinsonism, akinesia, increased severity of disability, anxiety and psychosis.

The definition of early-onset PD differs widely among studies, with ages ranging from 50 to 65 years; this may account for some of the studies that show no differences between early- and late-onset PD.[8] In studies that show positive differences, younger patients with PD experienced twice the frequency of depression than older patients.[10-13] Younger patients with PD and depression are more likely to have experienced depression before the onset of PD, to have a family history of PD and to manifest less motor impairment compared with older patients with PD and depression.[14] In addition, the depression scores of younger patients with PD correlated more closely with their degree of cognitive impairment; this implies that depression in this patient group may have a different aetiology to the depression in those with later onset of PD.[12] Postmortem studies show no neuropathological differences between patients with early- versus late-onset PD.[14]

From a psychosocial perspective, patients with early-onset PD are particularly vulnerable to depression as a reaction to the illness' detrimental effect on their careers, financial security and quality of life during their most productive years.[15] The early onset of PD causes 'premature social aging', whereby the level of social handicap is inconsistent with the patient's age and may further contribute to the risk factors for depression.[16]

Studies have indicated that there is a possible female-gender predisposition to depression with PD; in 1 study, 50% of the women with PD in their sixth decade had depression compared with 30% of age-matched men with PD.[17] When compared with the more disparate prevalence of a major depressive episode in older patients without PD (0.9 per 100) for women and 0.4 for men), the female-gender predisposition in PD seems diminished.[18]

Studies of depression in patients with hemiparkinsonism have not defined a consistent difference between patients affected on one side of the body only. A positive correlation between depression and unilateral motor changes would support the hypothesis of a laterality of structures mediating mood states.[19] Some studies have found an association between depression and right-sided hemiparkinsonism. The determination of this relationship appears to depend largely on the screening tool used to assess depression; patients with right-sided hemiparkinsonism had significantly more depressive symptoms when assessed using the Hamilton Depression Rating Scale (HDRS), but not when using the Geriatric Depression Scale.[10] The alteration of mood using focal transcranial stimulation may provide additional information regarding laterality (section 4.8).

The increasing severity of disability, especially due to akinesia, is associated with minor depressive episodes but not sustained major depression.[16,20] Symptoms with the strongest correlation to depression include bradyphrenia, lack of initiative, inhibited drive and thinking, and apathy.[20] Major depression occurs in 40 to 60% of patients with advanced PD who are not receiving antiparkinsonian treatment, regardless of the duration of illness or degree of physical disability.[8] Physical improvement after the successful treatment of PD has not reduced depression consistently.[16]

Originally, depression was thought to be related to the use of levodopa to treat PD.[8] Depressed patients with PD take significantly higher dosages of levodopa for a longer period of time than non-depressed patients.[21] Furthermore, patients with PD who are taking levodopa have significantly higher depression scores, when assessed with the Minnesota Multiple Personality Inventory (MMPI), compared with healthy controls without neurological disease.[8] However, many patients who experienced depression after taking levodopa had a history of depression that predated treatment.[22] Antiparkinsonian treatment with levodopa may indirectly interfere with serotonergic function in the CNS by its competition for uptake, storage and metabolism.[23] Treatment with antidepressants reverses the effect of levodopa on serotonin (5-hydroxytryptamine; 5-HT).[24] Some patients manifest depressive episodes if levodopa fails to show antiparkinsonian efficacy.[23] Occasionally, patients with a previous history of depressive episodes have attempted suicide while on levodopa.[25] The precipitation or exacerbation of depression by levodopa cannot be excluded but, in most patients, the mood changes have alternative explanations. If depression occurs, it responds to a reduction in the dosage of levodopa.[22]

Depression in patients with PD correlates with higher rates of anxiety and psychosis. When compared with depressed patients with multiple sclerosis, depressed patients with PD differ in having a higher frequency of episodes of atypical panic and anxiety.[26] Anxiety in PD manifests as panic disorder, phobias or a generalised anxiety disorder.[27] Unlike

depression, which may predate PD symptomatology, anxiety tends to appear after the onset of the motor abnormalities of PD.[27] In some patients, anxiety may sometimes be an adverse effect of antiparkinsonian treatment.[26,28,29]

Tandberg and colleagues[30] discovered a correlation between depression and thought disorder, which indicated that patients with PD and psychosis are more depressed than those without symptoms of psychosis. Clinicians should take care to establish whether a suicidal tendency in patients with PD is a response to a drug-associated psychosis or a depressive symptom.

1.2 Cognition and Depression

Depression can impair cognition in patients with PD, but without dementia. Depression in PD is attended by more cognitive deficits than are found in nondepressed patients with PD when matched for age, gender and severity of disease.[31-33] The performance of patients with PD and depression is worse than that of nondepressed patients with PD on registration memory tasks and shifting cognitive sets.[34] Patients with PD and depression perform better on short term memory tasks than depressed patients without PD and respond well to encouragement.[35]

Dementia is common in advanced PD and may be a risk factor for depression; however, in most studies, depression is equally frequent in PD with and without overt dementia.[36]

1.3 Relationship to the 'On-Off' Phenomenon

Fluctuation in mood may accompany the late-stage, sudden fluctuations in parkinsonism called the 'on-off' phenomenon.[4] Modified Zung Depression Scale scores drastically worsen and motor disability scores increase abruptly during 'off' periods.[4] Stabilisation of extrapyramidal symptoms may improve depression. One case report describes rapid-cycling, bipolar mood shifts during one patient's 'on-off' cycle.[37]

The pathophysiology of the 'on-off' phenomenon may depend upon the dopamine or noradrenaline (norepinephrine) neurotransmitter systems. Markedly reduced CSF dopamine- β -hydroxylase activity has been reported in patients during severe 'freezing' episodes.[38] While fluctuations in dopamine could account for the motor impairment, Sandyk[38] proposes that the locus ceruleus becomes deregulated, resulting in 'on-off' extrapyramidal symptoms, fluctuations in autonomic function, mood changes and sensory symptoms.

1.4 Metabolic Studies of Depression in PD

Of the functional neuroimaging studies, only positron emission tomography (PET) studies show a localised abnormality in depressed patients with PD. When evaluated by fluoro-deoxyglucose PET, depressed patients with PD show a lower rate of metabolism in the caudate and inferior orbitofrontal cortex, compared with both nondepressed patients with PD and healthy controls.[39] HDRS scores correlate positively with the severity of hypometabolism in the orbitofrontal cortex.[39] Orbitofrontal hypometabolism may reflect impaired dopaminergic stimulation from the ventral tegmental area.[39]

Single photon emission computed tomography (SPECT) has shown conflicting and inconsistent patterns of regional cerebral blood flow in depressed patients with PD. Concomitant dementia in some of the patients with PD who were tested may have confounded these studies.[40] Resting state regional cerebral blood flow as measured by PET, however, reveals bilateral reductions in flow in the medial prefrontal cortex (Brodmann's area 9) and contiguous cingulate cortex (Brodmann's area 32). These abnormalities have also been found in depressed patients without PD,[41] suggesting that there exists a common biological substrate between endogenous depression and the depression of PD.

2. The Importance of Diagnosing Depression

Treatment of depression in patients with PD may significantly slow cognitive decline, deterioration in Activities of Daily Living (ADLs) and progression to the more advanced of the Hoehn and Yahr stages. A longitudinal study by Starkstein and colleagues[42] showed that patients with major depression and PD showed a significantly greater decline in ADLs over a 1-year period than patients with PD with minor depression only or no depression. Patients with major depression and PD had significantly longer durations of illness, but when patients were matched for duration and followed longitudinally, those with major depression worsened to a significantly greater extent. Cost-benefit analyses of antidepressant treatment in patients with PD are urgently needed.

2.1 Definitions and Assessment

Depression as seen in PD may be classified as major depression, dysthymia or an organic mood syndrome, according to DSM-III-R,[5] or as a mood disorder caused by a general medical condition, according to the fourth edition of the same manual (DSM-IV).[43]

Depression may be difficult to recognise in patients with PD because the signs of the 2 disorders overlap. Akinesia can limit the range of facial expression, giving the patient an apparently depressed affect. Hypophonia and bradykinesia resemble the psychomotor retardation syndrome of depression, contributing to the appearance of sadness. Patients may also withdraw from their usual activities because of disability or social embarrassment regarding their condition. These signs of PD may mask underlying depression or, alternatively, clinicians may overdiagnose depression and undertreat PD.

Parkinsonism may artifactually inflate depression scale scores.[8] The scales used in most studies include the Beck Depression Inventory (BDI), HDRS, the Zung Scale and MMPI.[8] Although the items in the BDI might appear to confound motor impairment and mood changes, analysis supports the validity of this measure of depression.[36] The HDRS has been used more extensively in recent research. Studies that compare patients who have PD with controls who do not have PD or who do not have depression may not be as valid.[8] Cross-sectional studies may not detect successful treatment for depression as effectively as longitudinal reporting.

2.2 Research Criteria for PD

Tandberg and colleagues[30,44] divided a group of patients with PD into the diagnostic categories of definite, probable or possible PD. Those with possible PD more commonly had depression than those with more certain diagnoses.[30] A recent multicultural community study assessed the clinical features that are most practical in diagnosing PD. The study found that, after other causes of PD have been excluded, using at least 2 features from resting tremor, bradykinesia or rigidity allows reasonable diagnostic accuracy and estimation of prevalence.[45]

Dexamethasone suppression tests (DST) in patients with PD reveal that 10 to 44% have nonsuppression: higher rates of suppression occur in depressed compared with nondepressed patients with PD, but the test lacks sensitivity and specificity.[46] Authors agree that this diagnostic test is of little use for PD, as are the thyrotropin-releasing hormone and levodopa stimulation tests.[46-49]

3. Neurobiological Basis of Depression in PD

In general, CNS levels of dopamine, serotonin, noradrenaline and acetylcholine are decreased in patients with PD.[24] Depression has been associated with deficiencies of the first 3 of these transmitters.[8]

3.1 Dopamine

Since dopamine deficiency is the main feature of PD, studies have focused on defects in the mesolimbic dopamine system as being a potential correlate of behavioural changes.

A circuit connecting the ventral tegmental area to the orbitofrontal cortex may play a role in depression in PD. Parkinsonian degeneration of neurons in the ventral tegmental area, locus ceruleus, dorsal raphe and their cortical projections, results in remote derangements in basotemporal limbic regions. These derangements further disrupt basal ganglia-thalamo-cortical circuits and indirectly involve serotonergic neurons by disrupting orbitofrontal projections to the dorsal raphe.[50] The cells of the ventral tegmental area that serve as the origin of the mesolimbic dopaminergic projection have a decreased tyrosine hydroxylase activity in patients with PD, indicating a decreased dopaminergic output to cingulate, entorhinal and frontal cortices.[51] In addition to a decreased synthesis of dopamine in the ventral tegmental area, patients with PD undergo a greater loss of A10 dopaminergic neurons in this area than would be expected with normal aging.[15]

According to a 2-pronged model of dopamine deficiency in depression, dysfunction in the dopamine-mediated reward system induces anhedonia (the 'reduced capacity to experience reward or pleasure'[52]), while the dysfunction of serotonin pathways exacerbates abnormalities in the levels of dopamine via neurotransmitter interactions. Anhedonia may reflect a dysfunction in positive reward mechanisms, whereas negative reward systems are mediated by opioid receptors and may contribute to the dysphoric component of depression.

The dopaminergic reward system hypothesis of depression in PD is supported by the observed decrease in self-stimulation and cocaine usage in rats after the induction of lesions

in the ascending projections of dopaminergic neurons or the nucleus accumbens.[52] Similarly, patients with depression and PD demonstrated significantly less euphoria when given intravenous methylphenidate compared with nondepressed patients with PD and an equal level of physical disability.[53] Impressively, the depressed patients with PD registered even less euphoria than depressed patients without PD,[53] suggesting that depression in PD has unique pathobiological features.

The prefrontal/anterior cingulate circuit bears functional relevance to depression via the ventral striatum, which mediates the initiation of actions based on emotional stimuli. If this axis is dysfunctional, emotionally motivated behaviours are reduced, causing apathy and diminished motivation.

The surprising absence of correlation between CSF levels of the dopamine metabolite homovanillic acid and depression in patients with PD seems to dissociate major depression from brain dopamine levels.[54-56] This suggests that other conditions contribute to the mood disorder.

3.2 Serotonin

Damage to serotonergic neurons is not as pervasive as dopaminergic system damage in PD; [46] however, rostral cell groups lose up to half of their large neurons.[57] These include the dorsal raphe and the median raphe, which send serotonergic projections to diencephalic and limbic structures.

The role of serotonergic deficiency in depression in patients with PD has not been established. Serotonin reuptake sites are abnormally reduced in patients with PD, regardless of mood state.[58] Citalopram binding at serotonin reuptake sites and levels of 5-hydroxyindoleacetic acid (5-HIAA; the principle metabolite of serotonin) in both depressed and nondepressed patients with PD are abnormally reduced.[59,60] Affected areas include the frontal poles, temporal poles and putamen.[59-61] Whether the alteration of serotonergic receptor activity is a primary or secondary effect of PD remains unresolved.

Studies on the CSF of depressed patients with PD support the role of serotonin deficiency. CSF levels of 5-HIAA are low in depressed patients with PD.[47,54,55,62,63] Reduced levels of 5-HIAA are also seen in nondepressed patients with PD, but levels are lowest in patients with PD who meet the DSM-III criteria for major depression.[47,55] Dysthymic patients with PD showed no greater reduction in CSF levels of 5-HIAA than nondepressed patients with PD.[47] Low CSF levels of 5-HIAA often appear in depressed patients with PD, but do not correlate with depression.[47,64] Some symptoms of depression, namely psychomotor retardation and loss of self-esteem, correspond with lower CSF levels of 5-HIAA in patients with PD.[47] This raises the possibility of chemical-symptom correlates that are more specific than chemical-syndrome associations, and would allow combinations of neurotransmitter defects to produce mood disorders.

Alleviation of depression by orally administered 5-hydroxytryptophan (5-HTP), the precursor of serotonin, supports the possible efficacy of serotonin-directed antidepressant therapy; this effect was accompanied by a rise in CSF levels of 5-HIAA.[55] Controversial

studies exploring the links between personality traits and the risk of PD have raised the possibility that elderly patients with PD and premorbid extreme shyness are at a greater risk of depression and that this is mediated by serotonin.[65,66]

3.3 Noradrenaline (Norepinephrine)

The locus ceruleus is the noradrenergic source for the CNS. Classical antidepressant treatment targets the noradrenergic system and has been helpful in treating depressed patients with PD. Such patients show extensive cell loss, both rostrally and caudally in the locus ceruleus, whereas patients with PD who do not have depression have relative sparing of caudal neurons. That difference between these 2 groups is of uncertain significance, since caudal neurons project to the spinal cord and would not seem to mediate mood.[67] Severe deterioration of the locus ceruleus occurs in patients with PD without clinical manifestations of depression,[38] but depression in patients with PD is accompanied by a greater loss of neurons in the locus ceruleus (up to 94.7% in patients with both dementia and depression). [67,68]

Degeneration of the locus ceruleus may create hypersensitive noradrenergic receptors to trigger the switch between 'on' and 'off' and to indirectly play a role in the mood swings and sleep disorders that accompany depression.[38] Bradyphrenia correlates positively with decreased CSF levels of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylene glycol.[24] A deficiency of noradrenaline probably contributes to the neurobiology of depression in PD.

4. Treatment of Depression in PD

Antiparkinsonian agents affect either dopaminergic or anticholinergic activity, and are prescribed in various combinations according to patients' needs.

Levodopa, when coadministered with carbidopa, enhances dopamine synthesis by providing more substrate. Levodopa/carbidopa is available in both regular and sustained-release forms. Amantadine acts presynaptically by stimulating an increase in the release of dopamine and inhibiting its reuptake. Pergolide and bromocriptine act directly at postsynaptic dopaminergic receptors. Pramipexole is a non-ergot dopamine agonist that binds to dopamine D₂ and D₃ receptors. Monoamine oxidase (MAO) inhibitors decrease the catabolism of dopamine and other catecholamines. Selegiline (deprenyl) inhibits MAO type B, whereas entacapone (OR-611) inhibits catechol-*O*-methyltransferase (COMT), another enzyme that catabolises dopamine.

Anticholinergic medications, such as benztropine (bentropine) and trihexiphenidyl (benzhexol), decrease the tremor component of PD. Outside the US, biperiden is also used as an anticholinergic agent.

Surgical intervention for PD entails pallidotomy, thalamotomy, and transplantation or implantations of deep brain stimulators.

4.1 Antiparkinsonian Treatment

Mood responses to antiparkinsonian treatment are limited with respect to dopaminergic therapies, but MAO inhibitors and COMT inhibitors show promise as antidepressants (table I), possibly because of their combined effect on several catecholamines. As an antidepressant, levodopa has proven ineffective.[15,69] When levodopa was given to depressed patients without PD, only 22% showed a consistent improvement, even when large dosages were given in tolerable, gradual increments.[23]

In one study,[70] bromocriptine administered at a dosage of 85 to 220 mg/day produced significant improvements in symptoms of both PD and depression. However, not all patients experienced both of these effects, indicating that, at best, bromocriptine may have an adjunctive role in therapy for depressed patients with PD.[70] Bromocriptine inhibits the release of dopamine when given in low dosages, but in the higher dosages used for antiparkinsonian treatment, it increases postsynaptic dopamine activity,[70] possibly compensating for dopaminergic reward system dysfunction. Pergolide has no effect on depression in PD.[28] Bromocriptine and quinpirole, another dopamine agonist, reverse stress-induced anhedonia in rat models.[71] The antidepressant effect of pramipexole has not been reported.

The dopaminergic treatment amantadine alleviates the symptoms of depression in elderly patients without PD who do not meet the criteria for major depression.[24,43] Amantadine has indirect dopaminomimetic activity as an *N*-methyl-D-aspartate (NMDA) receptor antagonist: its central sympathomimetic actions in animal models suggest that it may have an antidepressant role.[72]

Although the antidepressant mechanism of action of anticholinergic medications has not been elucidated yet, they relieve depression in some patients with PD. Biperiden and trihexyphenidyl can alleviate depression and occasionally induce euphoria.[24] One case report described the alleviation of baseline depression in a patient with PD when benztropine was added to a regimen of levodopa/carbidopa and fluoxetine.[73] The adverse effects of anticholinergic medications make them difficult to use in many elderly patients.

4.2 Selegiline (Deprenyl)

The enhancement of catecholamines in the nervous system has produced promising antidepressant effects. There are 2 types of MAO inhibitors, type A and type B. Type A inhibitors block the catabolism of noradrenaline and serotonin, and type B inhibitors block the catabolism of dopamine. Selegiline is an MAO type B inhibitor but, at dosages above 20 mg/day, it inhibits both type A and type B MAO.[24] At dosages above 30 mg/day, the metabolites of selegiline (amphetamine and methamphetamine) have significant psychotropic activity.[24,74] Since the L-isomer of amphetamine plays only a minor role in mood changes compared with the D-isomer,[75] the antidepressant activity of selegiline is mainly attributed to its² MAO-inhibiting properties.[76]

Late-life depression may be modulated by age-related increases in type B MAO activity, resulting in a relative depletion of dopamine.[77] This hypothesis gives credence to the derangement of dopaminergic systems as a contributor to depression. Under this assumption,

not only selegiline, but a number of other agents may prove to be useful for the treatment of depression in PD, namely: (i) ritanserin, a 5-HT₂ receptor antagonist that significantly activates dopaminergic neurons in the substantia nigra and ventral tegmental area; (ii) nomifensine, a tetrahydroisoquinoline that enhances dopamine activity, as well as being a potent noradrenaline uptake inhibitor and a relatively weak serotonin uptake inhibitor; (iii) tyrosine, the dopamine precursor; and (iv) bromocriptine.[77]

Patients with mild PD who do not yet require levodopa treatment have an enhanced sense of well-being while receiving selegiline, as indicated by improved scores on the mental scale of the Unified Parkinson's Disease Rating Scale.[78] In patients taking both selegiline and levodopa/carbidopa, selegiline improved PD and depression.[79] A French, multicentre, double-blind, randomised, placebo-controlled trial showed a significant improvement in HDRS scores after 3 months of treatment with selegiline 10 mg/day;[80] patients did not have particularly high HDRS scores on entering the trial, but no comment was made on whether any patients met the DSM criteria for depression. When evaluated by the Profile of Mood States (POMS), selegiline significantly decreased psychiatric disturbance in patients with PD: the patients' POMS scores rebounded after selegiline was discontinued.[76]

4.3 Other Monoamine Oxidase Inhibitors

Newer MAO inhibitors show antidepressant efficacy in animal models, but have not been well tolerated in patients with PD.

Nomifensine has an efficacy equivalent to that of imipramine in depressed patients without PD,[77] but its adverse effects include the aggravation of involuntary movements.[3] Phenelzine is another MAO inhibitor that has shown antidepressant efficacy in patients with PD when used with levodopa/carbidopa or amantadine.[81,82] The use of amantadine instead of levodopa as the antiparkinsonian component of treatment reduces the risk of hypertensive crisis in a patient receiving a nonselective MAO inhibitor. Bifemelane, an MAO inhibitor that is selective for noradrenaline reuptake, shows central activity and may have potential as an antidepressant in humans.[72]

The reversible type A MAO inhibitor activity of moclobemide increases central synaptic noradrenaline and serotonin levels;[83] in animal models of anhedonia, it has proved as effective as desipramine in its antidepressant effect.[84] Brofaromine is another reversible type A MAO inhibitor with additional serotonin reuptake-inhibiting properties.[83,85] Although it has not been tested as an antidepressant, evidence for its potential use includes: (i) effects on sleep similar to those of tricyclic antidepressants (TCAs) and classical MAO inhibitors; and (ii) displacement of ³H-cyanoimipramine from serotonin transporters in the rat brain.[85] Neither moclobemide nor brofaromine cause hypotension in animal models, and may spare human patients with PD the adverse effect of orthostatic hypotension that is seen with other antiparkinsonian agents and TCAs.[83]

4.4 Catechol-O-Methyltransferase Inhibitors

COMT inhibitors prevent dopamine catabolism. A COMT inhibitor combined with a type A MAO inhibitor would synergistically maximise the level of catecholamines in the CNS; however, the effect of the combined regimen on blood pressure or the occurrence of other

adverse effects has not been determined. COMT inhibitors given together with levodopa/carbidopa improved the performance of rats in models of depression, without augmenting locomotor activity. This indicates that the coadministration of COMT inhibitors and antiparkinsonian agents might have antidepressant effects in humans that are mediated by an increased dopaminergic function.[86]

Entacapone (a peripherally acting COMT inhibitor) and moclobemide (a type A MAO inhibitor) were well tolerated in healthy volunteers, but their administration did not result in elevated serum levels of noradrenaline or adrenaline (epinephrine) and this combination has not been used in trials in patients with PD.[87]

4.5 Surgery

Surgery for PD includes fetal mesencephalic tissue transplantation, pallidotomy, pallidal stimulation, thalamotomy and subthalamic stimulation. Of these, only fetal mesencephalic tissue transplantation has been reported to cause mood changes. Adrenal medullary tissue transplantation causes acute, reversible psychosis or delirium and has been abandoned as a treatment for PD.[88-90]

Transplantation of human fetal mesencephalic tissue for the treatment of PD caused depression and nonspecific emotional and behavioural symptoms on a long term basis (up to 1 year after surgery in patients without a prior psychiatric history).[89] This effect may have attended an episodic and drastic physical worsening in some of the patients. The reason for the difference in neuropsychiatric outcome between the transplantation of adrenal medullary tissue and fetal mesencephalic tissue is not known.[89]

Ventroposterior pallidotomy in 24 cognitively intact patients with PD did not cause depression.[90] Of patients with PD referred for thalamotomy, 63% had depression;[91] however, the author did not comment on the effect of the surgical procedure on their mood states. Transplant candidates should have a pre- and postoperative neuropsychiatric evaluation to facilitate the treatment of mood disorders.

4.6 Antidepressants

Antidepressant medications used in patients without PD include TCAs, selective serotonin reuptake inhibitors (SSRIs) and newer combined reuptake inhibitors (CRIs). Only TCAs have been assessed in double-blind, placebo-controlled studies in patients with PD. The antidepressant medications used in patients with PD are shown in table II.

4.6.1 Tricyclic Antidepressants—TCAs block the reuptake of serotonin and noradrenaline as well as producing a long term increase in their receptor sensitivities.[24] In addition, these antidepressants have dopaminergic effects. Typical adverse events pertinent to patients with PD include orthostatic hypotension and anticholinergic effects.[24] Nortriptyline 100 mg/day was effective in relieving depression and caused less orthostatic hypotension than imipramine.[24,92] Nortriptyline also has the advantage of having a defined therapeutic serum concentration that allows closer monitoring of the dosage.

Desipramine, a drug with a relatively low incidence of anticholinergic effects, affords moderate relief of depression when given at a dosage of 100 mg/day. This drug may exacerbate parkinsonian resting tremor because it stimulates the noradrenergic system.[24] Patients with PD and rigidity seem to be more responsive to imipramine,[24,93] and part of the utility of the latter may be attributed to its effect on parkinsonian rigidity and its relief of reactive depression.[94-96]

Amoxapine produces extrapyramidal effects, since its second major metabolite, 7-hydroxyamoxapine, has potent dopamine receptor antagonist activity and may worsen the movement disorder.[24,97]

Drug trials have not investigated the therapeutic potential of the TCAs amitriptyline or protriptyline, or the tetracyclic antidepressant maprotiline.

4.6.2 Serotonergic Agents—Although SSRIs have shown efficacy in the treatment of depression, and neurobiological studies support a serotonergic hypothesis for depression in patients with PD, SSRIs have not been thoroughly tested in depressed patients with PD. SSRIs offer a benign adverse effect profile for this population, as they:[24]

- do not affect cardiac conduction
- do not decrease seizure threshold[98]
- exert minimal quinidine-like effects
- do not alter blood pressure.[99]

The main contraindication to the use of SSRIs in patients with PD relates to competition for metabolism by the cytochrome P450 (CYP) system, which increases the risk of toxicity in patients receiving concomitant therapy. One of the P450 isoenzymes, CYP2D6, metabolises TCAs, haloperidol, perphenazine, thioridazine, metoprolol, some antiarrhythmics, opioids, methamphetamine, vinblastine and phenytoin.[99] SSRIs vary in their competition for this enzyme: sertraline causes relatively less inhibition of CYP2D6 than fluoxetine or paroxetine. [99] SSRIs administered in combination with MAO inhibitors or TCAs may cause a 'serotonin syndrome', as discussed in section 6.2.1.

The SSRI fluvoxamine was effective in a patient with PD who had previously undergone electroconvulsive therapy (ECT) for depression.[100] When placed on a tryptophan-depleting diet, this patient experienced a recurrence of depression, which responded favourably to fluvoxamine.[100] Fluvoxamine inhibits CYP1A2, which catalyses a minor step in the metabolism of TCAs. In patients with low activity of the major metabolising enzyme of TCAs, CYP2D6 (a situation that occurs in 5 to 6% of the Caucasian and African-American populations), fluvoxamine could produce TCA toxicity at low dosages of TCAs. [99]

Despite its generally desirable adverse effect profile, fluoxetine reduced HDRS scores by only 2 to 3 points during treatment lasting more than 8 weeks. Furthermore, it has been reported to cause symptoms of PD, including tremor, akathisia, resting tremor, bradykinesia and dystonia.[24,101]

Buspirone 15 mg/day has no effect on depression in patients with PD.[24] Patients with PD, but without depression, have experienced significant worsening of disability and anxiety ratings when given buspirone, even though it has dopaminergic agonist effects similar to amfebutamone (bupropion). The anxiety was attributed to central noradrenergic stimulation, as opposed to dopaminergic agonism.[102]

Table III summarises the interactions between antiparkinsonian and antidepressant medications. Fluoxetine may worsen PD (table I) and other SSRIs may cause akathisia. Four patients experienced an increase in motor disability (resting tremor and akinesia/bradykinesia) when given fluoxetine for the treatment of major depression.[101] Worsening of PD caused by the dopamine-antagonising activity of fluoxetine has been reported 10 to 14 days after initiation and remits after withdrawal of the medication.[101] Akathisia is the most common neurological symptom caused by SSRIs in patients of any age and responds to a reduction of the dosage of SSRI medication or the addition of propranolol at low dosages.[99] A 'serotonin syndrome' attributable to the combined use of an SSRI and either a TCA or MAO inhibitor has been reported.

Double-blind studies involving these agents are addressed in section 5.

4.6.3 Newer Antidepressants—Newer antidepressant medications, such as venlafaxine, nefazodone and mirtazapine, have appealing pharmacokinetic profiles and may be effective against depression in patients with PD.

Venlafaxine, a CRI with both serotonergic and noradrenergic effects, has no apparent contraindication to its use in patients with PD.[97] The drug offers reduced CNS and cardiovascular toxicity,[98] but patients may develop sustained diastolic hypertension.[98] A significant antidepressant response occurred after only 2 weeks of treatment with venlafaxine in elderly patients, suggesting that this agent may produce more immediate clinical improvement than conventional antidepressants.[98] Unlike the SSRIs, venlafaxine is only weakly bound to plasma proteins, but its most common adverse effects are similar to those of the SSRIs (nervousness, sweating, nausea, sedation, anorexia, dry mouth and dizziness).[99]

Nefazodone, a chemical analogue of trazodone, has relatively greater serotonergic than noradrenergic activity. It increases serotonin levels both presynaptically and postsynaptically,[99] and is thus more than simply an SSRI. Nefazodone 100 to 500 mg/day was equivalent to imipramine in antidepressant effect, but was superior in terms of adverse effects in depressed patients without PD.[103] Owing to its short half-life and weak noradrenergic activity, nefazodone is less likely to produce sedation or orthostatic hypotension than trazodone and may be better tolerated by elderly patients.[98,99] Because of differences in CYP isoenzyme metabolism, switches from SSRIs to nefazodone may result in transient anxiety and agitation.[99]

Mirtazapine directly increases noradrenergic neurotransmission by direct antagonism of α_2 -adrenergic autoreceptors and indirect enhancement of serotonin 5-HT₁ receptor-mediated serotonergic neurotransmission.[104] A meta-analysis of pooled data from depressed

patients of all ages showed that mirtazapine has a sustained antidepressant efficacy, equivalent to that of amitriptyline, when depressed patients without PD are followed using HDRS scores.[105] These patients tolerated mirtazapine much better than amitriptyline or doxepin, and displayed no anticholinergic, adrenergic or serotonergic adverse effects. [104,106] Patients most commonly complained of sedation.[104] One consideration for patients with PD is that plasma concentrations of mirtazapine tend to be higher in the elderly.[104] Dosage reduction may therefore be appropriate.

4.6.4 Novel Antidepressant Medications—Other medications, such as the atypical antidepressants or agents that act on dopamine, opioid or neuropeptide receptors may have applications based on the neurobiology of PD and depression. The application of these agents has not yet been comprehensively studied in this setting.

Amfebutamone is a monocyclic antidepressant with indirect dopamine agonist properties. [24] When given to patients with PD receiving levodopa or trihexiphenidyl, amfebutamone improved depressive symptoms, but the response was limited in fewer than half of the depressed patients.[107] Amfebutamone has shown better efficacy in treating the motor manifestations of PD than it has as an antidepressant.[107] Adverse effects that limit the tolerable dosage of amfebutamone include elevated blood pressure,[99] nausea, vomiting, restlessness, postural tremor, hallucinations, confusion, psychosis, dyskinesias[24,107] and seizures.[108] Once the risk factors for epilepsy have been eliminated, the incidence of seizures approximates that of seizures caused by high dosages of TCAs (>200 mg/day).[99]

Captopril has shown antidepressant activity in rat models of depression using a learned helplessness paradigm.[109] Captopril is most commonly used as an ACE inhibitor for patients with hypertension, but also has an influence on the central opioid system, since its effects can be reversed with naloxone. In addition, it has an effect on monoamine neurotransmitters.[109]

Substance P-containing neurons can modulate dopaminergic cells in the substantia nigra, nor-adrenergic neurons in the locus ceruleus and serotonergic neurons.[110] Theoretically, tachykinin antagonists would allow the exogenous manipulation of neurotransmitter levels. One drawback of these antagonists, however, is the susceptibility of their peptide structure to enzymatic degradation, severely limiting *in vivo* potency.[110] The use of substance P antagonists has not been investigated in patients with PD.

Treatment guidelines for depression in patients with PD lack the benefit of a placebo-controlled, double-blind assessment of antidepressant efficacy. The ideal antidepressant for patients with PD would inhibit dopamine, serotonin and noradrenaline reuptake, without causing acute hypertensive adverse effects. It would not be metabolised by CYP2D6 and would have a stable pharmacokinetic profile in the elderly. A moderately long half-life would allow once-daily administration and there would be few drug-drug interactions. Double-blind, placebo-controlled studies on the CRIs will reveal whether the ideal antidepressant for patients with PD already exists.

4.7 Electroconvulsive Therapy

The use of ECT has proven efficacious as antidepressant therapy, but requires special considerations in patients with PD. ECT is useful if patients are suicidal or cannot wait the required time for a response to antidepressant medication.[24] ECT may also be useful for patients with PD who are not depressed, but who experience the 'on-off' syndrome or are unresponsive to treatment for PD.[111] ECT has been used to treat mania in patients who were given levodopa.[28,111,112]

Seven depressed patients with PD had their mean HDRS scores reduced from 65 to 27 after having 7 bilateral ECT treatments each.[113] However, patients may relapse into a depressive episode from 1 week to 6 to 12 months after ECT.[113,114] Motor symptoms respond sooner than depression to ECT, and the motor symptoms also relapse more quickly. [114-117] Despite its adverse effects (amnesia, disorientation, slurred speech, tremors, increased intraocular pressure, urinary retention, paralytic ileus[111] and worsening of tardive dyskinesia[114]), ECT has better efficacy and tolerability than TCA therapy. [111,113,118] Patients with rigidity responded better to ECT than those with tremor-dominant PD with regard to motor and depressive symptoms.[119]

The antiparkinsonian effects of ECT involve the dopaminergic and serotonergic pathways. ECT enhances dopamine transmission in animals, possibly through increased endogenous MAO inhibitor activity. In addition, ECT reduces the pathological increase in opioid system function, which in turn increases striatal and mesolimbic dopamine release. ECT downregulates presynaptic 5-HT_{1A} receptors and upregulates postsynaptic 5-HT₂ receptors. This serotonergic effect of ECT is considered to contribute significantly to its antidepressant activity. In patients with PD, a lack of elevated levels of CSF homovanillic acid after ECT reduces the likelihood of noradrenergic effects caused by ECT.[117,120]

Unfortunately, while depression and akinesia in patients with PD are improved by ECT, patients are more susceptible (compared with depressed patients without PD) to prolonged delirium after unilateral and bilateral ECT.[113,121] Injury to the basal ganglia, as indicated by T₂-weighted magnetic resonance imaging hyperintensities (specifically in the caudate), may predispose the elderly to develop a reversible, interictal delirium during a course of ECT.[122] Furthermore, multiple ECT treatments increase the duration of delirium (up to 21 days) and preprocedural atropine may contribute to confusion;[121] however, bilateral electrode placement may be less deleterious than unilateral placement.[121]

4.8 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) has provided temporary relief from depression under experimental conditions. TMS exposes focal regions of the brain to magnetic and electrical energy that does not cause structural change, but does induce functional changes. It produces transient alterations in both motor function and mood in patients with PD.[123] Drawbacks to using TMS include a temporary therapeutic effect, a muscle tension-type headache at the site of stimulation and a risk of seizures.[123]

Electromyography performed simultaneously with rapid-rate TMS (rTMS) shows that patients with PD have a prolonged excitable period preceding the motor evoked potential,

and this prolongation may be remedied by rTMS, thus alleviating akinesia.[123] Researchers have been able to induce subjective 'sadness' by administering rTMS to the left prefrontal areas, whereas 'happiness' results from stimulation of the right prefrontal areas.[123] Sandyk and Derpapas[124] noted that relaxation, sleepiness, mood elevation, increased dreaming and enhancement of activities in the electroencephalogram resulting from external application of pT-range magnetic fields have also been noted in healthy individuals taking melatonin, and they proposed that these effects were mediated by the pineal gland. While this remains speculative, there is a significant rise in the plasma level of prolactin after TMS, which would indicate an effect on the hypothalamic tuberoinfundibular dopaminergic system.

5. Clinical Drug Trials

According to a meta-analysis of controlled antidepressant drug trials, reported trials of antidepressants in PD were not successfully blinded.[92] The trials tested TCAs, monocyclic antidepressants and selegiline for the treatment of depression in PD. Studies of serotonergic and adjuvant antiparkinsonian medications are needed in this indication.

Klaassen et al.[92] identified clinically meaningful design criteria for future studies, which included:

- randomised treatment allocation
- blinded allocation procedure
- enrolment of 75 individuals per study group
- minimal bias from withdrawals
- close follow-up
- no addition of co-interventions or at least comparable co-interventions in both comparison groups
- adequate outcome measures
- generation of an adverse effect profile
- intent-to-treat analyses.

Of the 12 studies that were deemed to be adequate, 5 tested selegiline and the others investigated amitriptyline, clomipramine, nortriptyline, desipramine, imipramine, amfebutamone and nomifensine.[92] Five of 12 studies had positive outcomes (table IV), and these involved selegiline (10 mg/day), nortriptyline (100 mg/day), desipramine (100 mg/day), imipramine (given on an age-based sliding scale dosage) and amfebutamone (to a maximum of 450 mg/day).[92]

Longitudinal follow-up of patients with PD over a mean of 2.5 years revealed that depression remitted in only 4 of 21 patients: 1 spontaneously, 2 with standard antidepressant treatment and 1 with 5-HTP.[55] This indicates the necessity of developing an antidepressant treatment with long term effectiveness in patients with PD.

6. Special Considerations

6.1 Elderly Patients

Depression in the elderly causes significant morbidity and mortality and is difficult to treat. The cumulative risk of depression in individuals born between 1915 and 1945 has reached 30%. [15] When untreated, major depression in the elderly leads to significantly increased mortality. [98] However, treatment with TCAs or ECT must be carried out judiciously in the elderly, noting their increased pharmacodynamic sensitivity, slower clearance of drug metabolites and potentially higher plasma drug concentrations. [98] Because of an increase in the fat: muscle ratio in the elderly, the volume of distribution of psychotropic medications is higher. [98]

Anticholinergic effects are less well tolerated by elderly patients; patients may develop urinary retention, blurred vision, paralytic ileus, faecal impaction and a dry mouth that prevents them from comfortably wearing dentures. [98] In general, patients aged >75 years receive only a modest therapeutic effect from antidepressants. This patient group also contains a subgroup of very severely depressed, refractory individuals with complicating medical illnesses, which creates a further challenge for the physician. [98] Extrapyramidal symptoms respond better to ECT in older patients than in younger patients. [113]

6.2 Other Factors

6.2.1 Risk of Coadministering Selegiline and Antidepressants—A ‘serotonin syndrome’ occurs infrequently with the coadministration of selegiline and TCAs; however, the US Food and Drug Administration (FDA) recommends against giving an antidepressant (TCA or SSRI) and selegiline simultaneously. The manufacturer of selegiline has distributed warnings of possible CNS toxicity, approximating to the ‘serotonin syndrome’, which occurs when this MAO type B inhibitor is administered with a TCA. The ‘serotonin syndrome’ comprises hyperpyrexia, tremors, agitation, restlessness and decreased mental status, but has rarely proven fatal.

A recent review of published case reports of adverse experiences showed that 0.24% of patients experienced symptoms possibly consistent with the ‘serotonin syndrome’. Of those 11 patients, only 2 had symptoms rated as ‘serious’. [133]

Another review of 28 patients with PD taking selegiline and one other antidepressant found no selegiline interactions. The adverse effects reported have been manifested commonly by patients receiving antidepressant monotherapy. [134]

6.2.2 Anticipated Effects of Chronic Pain—King [135] points out that chronic pain is a common symptom of PD and that its impact on depression must be considered in the comprehensive treatment of depression in PD.

6.2.3 Treatment of Anxiety—The treatment of anxiety in patients with PD addresses the possible relevance of deficiencies in serotonin, noradrenaline, and γ -aminobutyric acid (GABA). Low CSF levels of 5-HIAA and, therefore, of serotonin correlate with clinical measures of anxiety, psychomotor retardation and insomnia in depressed patients without

PD.[136] Noradrenaline and GABA levels are also abnormal in patients with PD who have anxiety.

Therapy with nortriptyline, desipramine, imipramine and fluoxetine may be beneficial for patients with both anxiety and depression, since these drugs are effective in the treatment of panic disorder.[24] Patients with panic disorder who are exposed for the first time to antidepressants may be sensitive to the stimulating effects of these drugs; benzodiazepines may alleviate these effects and may be used adjunctively until the symptoms of panic resolve.[24] Alternatively, buspirone may also be used with TCAs if generalised anxiety is present.[24] Selegiline may not be as effective in depressed patients with anxiety or panic. [137]

7. Algorithmic Approach

Figure 1 outlines an algorithm for the pharmacological treatment of depression in patients with PD.

The following factors should be considered in conjunction with the algorithm.

1. Each antidepressant medication should have a 6-week trial at the maximum tolerated therapeutic dosage or at the appropriate plasma concentration.[24]
2. More studies have focused on proving the efficacy of TCAs than SSRIs, but the adverse effect profile for SSRIs is more favourable for patients with PD.
3. Once adequate antidepressant therapy has been achieved, medications should be continued for 6 months before tapering of the drug dosage is attempted;[24] long term treatment may be necessary.
4. Consider augmentation with lithium, although it should be noted that lithium may cause adverse extrapyramidal adverse effects.

8. Conclusions

PD is a common neurological illness and various degrees of depression commonly complicate its course. Possible risk factors for developing depression with PD include: younger age, younger age at onset of PD, female gender, akinesia, increased severity of disability, anxiety and psychosis. Depression may be difficult to diagnose in a patient with PD because the signs of the 2 conditions overlap. Depression in patients with PD relates to deficiencies in dopamine, noradrenaline and serotonin.

Surprisingly, few placebo-controlled studies of antidepressant therapy in patients with PD exist. Of the therapeutic agents that have been studied, TCAs are effective, while selegiline has antidepressant properties, but is much more effective as an antiparkinsonian agent. Nevertheless, the neurobiology of PD and depression indicates that newer medications, including serotonergic agents and COMT inhibitors, offer a potential combined antiparkinsonian and antidepressant treatment.

A 'serotonin syndrome' has occurred frequently enough to preclude the coadministration of selegiline with SSRIs or TCAs. Multiple drug-drug interactions between antiparkinsonian and antidepressant medications, and the effects of polypharmacy on the elderly patient, complicate treatment strategies. Other somatic treatments for depression in patients with PD include ECT and, possibly, rTMS.

An algorithmic approach to the pharmacological treatment of depression in patients with PD requires the careful consideration of current antiparkinsonian medications, trial administration of SSRIs and TCAs, and consideration of the benefits of new serotonergic medications, MAO inhibitors and COMT inhibitors. At this time, there are no established first-choice antidepressant drugs for patients with PD, and randomised, double-blind, placebo-controlled studies are warranted.

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Fig. 1.

Treatment algorithm for depression in patients with Parkinson's disease (PD).[24]

Abbreviations: COMT = catechol-*O*-methyltransferase; CRI = combined reuptake inhibitor; ECT = electroconvulsive therapy; MAO = monoamine oxidase; SSRI = selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor; TCA = tricyclic antidepressant.

Table I

Antidepressant (AD) and antiparkinsonian (AP) effects of medications used or proposed for use in patients with PD

Drug	AD	AP	Comments
Antiparkinsonian agents			
Amantadine	+	Yes	Dopaminergic
Benzatropine (bentropine)	+	Yes	Anticholinergic
Biperiden	+	Yes	Anticholinergic
Bromocriptine	+	Yes	Dopaminergic
Entacapone (OR-611) ^a	?	Yes	Dopaminergic
Levodopa	0	Yes	Dopaminergic
Pramipexole	?	Yes	Dopaminergic
Selegiline (deprenyl)	– <i>b</i>	Yes	MAO-B inhibitor
Trihexyphenidyl (benzhexol)	+	Yes	Anticholinergic
Tyrosine	?	Yes	Dopaminergic
Tricyclic antidepressants			
Amitriptyline	+	×	Cholinergic
Amoxapine	?	×	Dopamine blockade
Clomipramine	–	?	
Desipramine	+	!	Tremor
Imipramine	+	Yes	Dopaminergic
Nortriptyline	+	!	Cholinergic
Protriptyline	?	×	Cholinergic
Selective serotonin reuptake inhibitors			
Fluoxetine	–	×	EPS
Fluvoxamine	+	?	
Monoamine oxidase inhibitors			
Brofaromine	?	?	
Moclobemide	?	?	
Phenelzine	+	×	EPS
New serotonergic and combined reuptake inhibitors			
Mirtazapine	+	?	
Nefazodone	+	?	
Nomifensine	+	Yes	Dopaminergic
Venlafaxine	?	?	
Other treatments			
Amfebutamone (bupropion)	++	Yes	Dopaminergic
Bifemelane	?	?	
Buspirone	–	No	Despite dopaminergic agonism
Captopril	?	No	
Cholecystokinin	?	No	
Lithium	+	×	EPS

Drug	AD	AP	Comments
Ritanserin	?	Yes	Dopaminergic
Tachykinin antagonists	?	No	
Trazodone	?	No	
Electroconvulsive therapy	+	Yes	Dopaminergic
Transcranial magnetic stimulation	+	Yes	

Abbreviations and symbols: EPS = extrapyramidal symptoms; MAO-B = monoamine oxidase type B; + = reported to have this effect; ++ = positive effect confirmed in placebo-controlled trial; - = ineffective; ! = worsens EPS; × = use contraindicated in patients with Parkinson's disease; ? = effect unreported.

^aCatechol-*O*-methyltransferase inhibitor.

^bSee text (section 5.2).

Table II

Antidepressant medications used in Parkinson's disease and their dosages

Generic name	Dosages [mg/day]	
	initial	maximum
Amfebutamone (bupropion)	100	450
Amitriptyline	75	150
Amoxapine	50	300
Desipramine	25	200
Doxepin	75	300
Entacapone (OR-611)	200	200
Fluoxetine	20	60
Fluvoxamine	50	300
Imipramine	75	150
Maprotiline	25	225
Mirtazapine	20	60
Nefazodone	200	600
Nortriptyline	75	100
Paroxetine	10	50
Phenelzine	45	15
Protriptyline	15	60
Selegiline (deprenyl)	10	30 ^a
Sertraline	50	200
Trazodone	50	600
Trimipramine	75	200
Venlafaxine	150	375

^aSelegiline 10mg is adequate for neuroprotection; 30mg may have antidepressant activity and requires that the patient maintains a low-tyramine diet.

Table III

Drug-drug interactions of medications used in Parkinson's disease and depression

Drug 1	Drug 2	Effect of interaction
Amantadine	Anticholinergic agents	Increased anticholinergic effect
Fluvoxamine	TCAs	Inhibited metabolism of TCA
Levodopa	Lithium	Increased extrapyramidal signs
Levodopa	MAOIs	Hypertensive reaction from increased levels of dopamine and noradrenaline (norepinephrine)
MAOIs	Methylphenidate	Hypertensive reaction from increased levels of dopamine and noradrenaline
MAOIs	SSRIs or TCAs	Serotonin syndrome
Methylphenidate	SSRIs	Inhibited metabolism of SSRIs
Nefazodone	SSRIs	Inhibited metabolism of nefazodone
Selegiline (deprenyl)	SSRIs or TCAs	Rare serotonin syndrome
SSRIs	TCAs	Serotonin syndrome caused by inhibited metabolism of TCAs

Abbreviations: MAOIs = monoamine oxidase inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

Table IV

Overview of placebo-controlled antidepressant trials for depression in patients with Parkinson's disease (after Klaassen et al.,[92] with permission)

Antidepressant	Number of patients	Outcome
Selegiline (deprenyl)[79]	28	–
Selegiline[80]	93	+
Selegiline[125]	27	–
Selegiline[126]	46	–
Selegiline[127]	18	–
Imipramine[96]	38	+
Amfebutamone (bupropion)[107]	14	+
Amitriptyline[128]	31	–
Clomipramine[129]	20	–
Desipramine[130]	39	+
Nomifensine[131]	8	–
Nortriptyline[132]	19	+

Symbols: + = positive antidepressant effect; – = no antidepressant effect.