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Depression in Patients with Parkinson's Disease

Epidemiology, Pathophysiology and Treatment Options

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Abstract

The evaluation and treatment of depression is an important component of the management of individuals with Parkinson's disease. This review summarises current knowledge on the epidemiology, pathophysiology and treatment of depression in Parkinson's disease.

Limited information is available regarding the pathophysiology of depression in Parkinson's disease and the effectiveness of treatment. Selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) are commonly used but more information is needed regarding their tolerability and antidepressant efficacy in patients with Parkinson's disease, and their effect on motor function.

Antidepressants can interact with selegiline (deprenyl) to cause the 'serotonin syndrome', although retrospective chart reviews indicate that this is rare. While several case reports have noted worsening parkinsonian motor features with SSRI use, open-label prospective studies have not substantiated these findings. Further double-blind, prospective studies would be valuable to further evaluate the tolerability and efficacy of antidepressants in Parkinson's disease.

The identification and treatment of depression is critically important in the management of Parkinson's disease. Depression in Parkinson's disease is very common and has a major impact on patients' quality of life. Reported prevalence rates range from 4 to 70%.[1] A recent study found that depression was one of the most detrimental factors impacting on overall quality of life in patients with Parkinson's disease.[2]

A recent survey by Parkinson's Study Group (PSG) investigators found that 26% of patients with Parkinson's disease are receiving antidepressants.[3] Despite widespread use, there is limited information available regarding the efficacy of antidepressants in Parkinson's disease. In addition, multiple case reports have suggested that selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) may worsen the motor features of Parkinson's disease. There is also concern that the concomitant use of selegiline (deprenyl; a monoamine oxidase inhibitor commonly used for the motor symptoms of Parkinson's disease) and an SSRI might cause the serotonin syndrome.

In this review, we summarise available information on the epidemiology and pathophysiology of depression in Parkinson's disease, review treatment options and discuss possible interactions between antidepressants and selegiline. This information may help guide clinical treatment and define the need for further studies.

1. Epidemiology

1.1 Diagnosis

Depression in Parkinson's disease can be diagnosed in accordance with criteria provided in the DSM-IV.[4] Many patients with Parkinson's disease appear to have depressive symptoms that do not meet DSM criteria for a major depressive disorder, but do meet criteria for less severe depressive disorders, such as dysthymic disorder and minor depressive disorder.[5]

Clinical rating scales can be used to quantify the magnitude of depression. Such scales include the Beck Depression Inventory (BDI),[6] the Minnesota Multiphasic Personality Inventory,[7] and the Hamilton Depression Rating Scale (HAM-D).[8] Other scales include the Montgomery-Åsberg Depression Rating Scale (MADRS),[9] the Geriatric Depression scale,[10] and the General Health Questionnaire.[11,12] The BDI and HAM-D are the two most commonly used rating scales to assess depression in individuals with Parkinson's disease.[13-17] The BDI has been found to be reliable and valid for quantifying depression in such patients.[18] Other instruments, including the HAM-D, have not yet been validated.

The somatic symptoms of Parkinson's disease, such as sleeping difficulties and psychomotor retardation, may overlap with depressive symptoms, often making it difficult to diagnose depression.

1.2 Prevalence

The incidence of depression in patients with Parkinson's disease varies widely depending on the criteria employed to diagnose depression. In early studies, the term 'depression' was loosely defined,[19] and patients were characterised as being depressed by self-reported rating scales and nonstandardised clinical interviews.[19] More recent studies have utilised DSM criteria and validated rating scales, resulting in more meaningful data.

Several reviews have found that 40 to 50% of patients with Parkinson's disease fulfil DSM-IV criteria for a mood disorder.[5,20-24] Approximately 20% of patients with Parkinson's disease meet criteria for major depression, while 20% meet criteria

for dysthymia.[5] However, the majority of these studies evaluated patients in tertiary care settings.[5,20-24] The prevalence figures are disputed by some investigators who argue that patients with Parkinson's disease who are in tertiary care settings may be more likely to experience depression than patients with Parkinson's disease who live in the community.[25] Indeed, a number of studies evaluating community-based populations have uncovered lower prevalence rates of depression in Parkinson's disease. Tandberg et al.[25] found a prevalence rate of only 7.7% for major depression using DSM-III criteria,[26] MADRS and BDI scores in a community-based study.[25] While 45% of patients with Parkinson's disease were found to have mild depression as determined by the MADRS, only 5.1% of these patients were moderately or severely depressed.[25] Hantz et al.[19] found that only 2.7% of patients with Parkinson's disease who were living in the community had major depression as diagnosed using DSM-III criteria. However, 16% of identified patients with Parkinson's disease refused to participate in this study and 26% of patients [those with Mini Mental State Examination (MMSE) scores less than 26] were excluded. This could be important as there may be an association between impaired cognitive function and major depression in Parkinson's disease.[27]

Limited studies suggest that depression may be slightly more common in female patients with Parkinson's disease.[28]

1.3 Depression and Age at Onset

There may be an association between age at onset and depressive symptoms in Parkinson's disease, although the issue remains controversial. Several studies have suggested that patients with Parkinson's disease who become depressed generally tend to be younger than those patients who do not become depressed.[29] However, Kostic et al.[30] found that although patients with early onset Parkinson's disease showed a higher frequency of depression when compared with a late onset group, the difference was not present after controlling for duration of illness.

1.4 Prodromal Symptoms

Several investigators have posited the existence of premorbid personality characteristics in patients with Parkinson's disease, including introversion and lack of flexibility.[31,32] Patients with Parkinson's disease may also demonstrate premorbid depressive characteristics. In one retrospective study of 60 patients with Parkinson's disease and 58 age-matched controls examining the decade prior to disease onset, patients with Parkinson's disease were found to consult general practice physicians for 'mood disorders' more frequently than the control group. 'Mood disorders' included depression, anxiety and nervousness.[33]

1.5 Symptoms

Depressive symptoms in patients with Parkinson's disease have some similarities to and some differences from those observed in patients without Parkinson's disease. Depression in both groups is characterised by loss of interest, loss of energy, psychomotor retardation, difficulty with concentration, irritability, sadness and dysphoria.[34,35] Depressed patients with Parkinson's disease exhibit less self-blame, guilt, sense of failure and delusional ideation,[36] and harbour fewer self-destructive thoughts than patients with primary depression.[24]

Although patients with Parkinson's disease may entertain suicidal thoughts, they seldom commit suicide.[37] Features of panic and anxiety commonly coexist with depression in patients with Parkinson's disease,[38] while episodes of mania and circadian mood changes do not.[34]

1.6 Depression and Severity of Parkinson's Disease (PD)

As early as 1923, Jackson et al.[39] reported that depression frequently preceded the onset of motor signs in individuals who developed Parkinson's disease. Subsequent studies have confirmed this finding, with prevalence rates of premorbid depression ranging from 12 to 37%.[40]

Depression in Parkinson's disease does not consistently correlate with severity of motor symp-

toms,[41] or functional disability.[42] Once motor symptoms emerge, there may be a nonlinear relationship of depressive symptoms to stage of disease. Two clinical studies have found depression to be most common in Hoehn and Yahr stages I, III and IV.[43,44] It is unclear whether this observation represents a consistent triphasic pattern, or whether methodological issues such as sampling bias could explain these findings.[45]

1.7 Depression and Motor Fluctuations

Motor fluctuations may be accompanied by fluctuations in mood. Several studies have noted a correlation between 'off' periods and depressive symptoms in small sample populations.[46-48] Depressed mood often improves as patients transition from the 'off' to the 'on' state. In addition, Menza et al.[46] described patients whose mood improved going from the 'off' to the 'on' state, only to have feelings of dysphoria recur as peak dose dyskinesias emerged.

1.8 Depression in PD Compared with Other Chronic Diseases

Depression may be more intimately linked to Parkinson's disease than other chronic, physically disabling ailments.[49,50] Patients with Parkinson's disease exhibit significantly more depression than age- and gender-matched patients experiencing a wide array of chronic diseases including rheumatoid arthritis, paraplegia[51] and hemiplegia due to cerebrovascular disease. Patients with parkinsonian symptoms exhibit more anxiety, general somatic symptoms and less motivation for work and other interests than patients with other disorders such as chronic disabilities, including cerebrovascular disease, spinal cord disease and orthopaedic conditions.[52]

2. Pathophysiology

Endogenous or reactive factors, or both, may cause depression in individuals with Parkinson's disease. Neither functional disability nor disease duration has been consistently associated with depression in Parkinson's disease. Thus, a simple reactive model appears unlikely as the predominant cause of depression in most cases. The occurrence of depression shortly before motor symptoms in a large proportion of patients (see section 1.6) argues for a biochemical aetiology. Nonetheless, a variety of factors, including biochemical changes and psychosocial issues, may affect mood, and one or the other may be dominant in a given individual.

2.1 Depression and Dopamine

Dopamine may play a role in the pathogenesis of depression in Parkinson's disease. Affective disorders have long been associated with CNS changes in catecholamine metabolism,[53-55] and depression has been linked to a relative deficiency of catecholamines. A reduction of catecholamines has been identified in patients with Parkinson's disease,[56] sparking interest in the aminergic hypothesis for depression in Parkinson's disease. Decreased CSF levels of homovanillic acid (HVA; a metabolite of dopamine) in depressed patients with Parkinson's disease have been reported,[57-59] but other studies have failed to replicate these findings.[60]

Parkinson's disease is caused by a progressive loss of dopaminergic neurons in the substantia nigra, resulting in striatal dopamine deficiency. Some psychiatric conditions, including depression[61] and bipolar disorder,[62] may be caused by a reduction of neurotransmitters, including dopamine. There is evidence that L-tyrosine and levodopa, precursors of dopamine, have antidepressant properties, particularly in patients with psychomotor retardation.[63-65] In addition, some antidepressants including nomifensine and amfebutamone (bupropion) function as dopamine reuptake inhibitors,[66] although it is unknown whether this mechanism of action is entirely responsible for the antidepressant activity of these drugs.[67]

Animal studies have focused on dopaminergic circuits for reward, using 'learned helplessness' as a possible model for reactive depression.[68] When exposed to uncontrollable stressors, animals develop decreased spontaneous activity and increased pas-

sivity. Although decreased levels of dopamine are found in the caudate nucleus and nucleus accumbens[69] of these conditioned animals, the validity of this model as a mechanism of depression remains controversial.[70,71]

Lesions of dopaminergic pathways outside the striatum have also been implicated in neuropsychiatric disorders.[72] In animal models, the ventral tegmentum plays a role in reward system behaviours.[73] Autopsies of several patients who had had depression and Parkinson's disease revealed dopamine depletion in the ventral tegmental area (VTA).[74] VTA afferents project to the orbital and prefrontal cortices.[75,76] Using 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), these regions have been found to be hypometabolic in depressed patients with Parkinson's disease.[77] Levodopa treatment has not consistently alleviated depressive symptoms,[78] suggesting that dopamine deficiency alone is an inadequate explanation for depression in Parkinson's disease.

2.2 Depression and Serotonin

Serotonergic dysfunction is thought to play a major role in the aetiology of depression, both in patients with and without Parkinson's disease.[78] The efficacy of SSRIs in treating depression underscores the importance of serotonin in depressive illness.

Alterations in CSF serotonergic parameters have been associated with depression in Parkinson's disease. Mayeux et al.[79] found a 50% reduction in CSF levels of 5-hydroxyindoleacetic acid (5-HIAA; a metabolite of serotonin) in patients with Parkinson's disease compared with healthy controls, while depressed patients with Parkinson's disease had CSF levels of 5-HIAA which were about 20% lower than nondepressed patients with Parkinson's disease.[79] Depressed patients without Parkinson's disease who attempted suicide reportedly had lower CSF 5-HIAA levels than controls.[80]

In a more recent study, Kuhn et al.[81] determined levels of biogenic amines in the CSF in 26 patients with early symptoms of Parkinson's disease who were not yet receiving antiparkinsonian treatment. No significant differences were found in CSF levels of dopamine, HVA or 5-HIAA between those patients with depression and those without. Thus, previously identified differences in CSF biochemical markers may be due to antiparkinsonian therapy,[81] and support for the role of serotonergic alterations in depressed patients with Parkinson's disease remains elusive.

2.3 Anatomy of Depression in PD

Anatomical research on depression has focused on the frontal lobes,[82-84] based primarily on animal models in which anterior cortical lesions cause apathy and emotional blunting.[85] PET studies have identified disturbances in the frontal lobes of depressed patients with Parkinson's disease.[77] The anteromedial regions of the medial frontal cortex and cingulate cortex (Brodman's areas 9 and 32) demonstrate reduced cerebral blood flow in depressed patients with Parkinson's disease compared with nondepressed patients with Parkinson's disease[86] and nondepressed healthy elderly controls. Similar findings have been reported in individuals who were not elderly and did not have Parkinson's disease.[87,88] Another study using hexamethylpropylene amine oxime spectroscopy (HMPAO-SPECT) yielded similar results.[89] Mayberg et al.,[77] using FDG-PET, identified hypometabolism of the caudate nuclei and anterior and orbitoinferior frontal cortices in depressed patients with Parkinson's disease compared with nondepressed patients and controls.[77]

There is some evidence that the brainstem plays a role in mood disorders. In one case report of deep brain stimulation in a woman with long-standing Parkinson's disease and no prior history of depression, transient acute depression was induced by high-frequency stimulation of the left substantia nigra, 2mm below the target site.[90] Subthalamic nucleus stimulation failed to elicit depressive symptoms. Although the aetiology of depression in this case in unknown, neural networks passing through the substantia nigra may have been affected.

Other evidence for brainstem involvement in depression includes a preliminary study using transcranial sonography (TS) that identified mesencephalic brainstem alterations in depressed patients with Parkinson's disease.[91] Increased raphe echogenicity was noted in depressed patients with Parkinson's disease compared with controls who were not depressed and did not have Parkinson's disease, similar to findings previously reported in depressed patients who did not have Parkinson's disease.[92,93] Additional blinded trials using TS are needed to confirm these early observations.

3. Treatment

3.1 Nonpharmacological

Psychological counselling may be of some benefit in treating depression in Parkinson's disease.[94] Ellgring et al.[94] recruited 34 patients with Parkinson's disease to complete self-reported questionnaires concerning mood changes, anxiety, worry and other psychosocial issues. After a period of individual counselling, patients reported significant improvement. However, standardised depression scales were not administered before and after counselling, and there was no control group.

3.2 Pharmacological

3.2.1 Antidepressants

Tricyclic Antidepressants

Early trials of tricyclic antidepressants (TCAs) suggested that they might improve parkinsonian motor features,[95,96] while other trials failed to note significant benefit. Denmark et al.[97] evaluated the effect of imipramine in nondepressed patients with Parkinson's disease in a double-blind, placebo-controlled crossover trial. All antiparkinsonian medications had been discontinued 3 days prior to the study, and improvement was noted in salivation and rigidity in 5 of 8 patients. In contrast, Andersen et al.[98] performed a double-blind, placebo-controlled crossover trial of nortriptyline in 19 depressed patients with Parkinson's disease who were optimally treated with levodopa/carbidopa. Nortriptyline produced no significant changes in motor signs, although depressive symptoms improved.

Varying results from early studies may be explained by differences in study design. Clinical observation was frequently used to document changes in depression and motor function, rather than clinical rating scales. In addition, patients who were suboptimally treated with antiparkinsonian medications often experienced improvement in motor signs, while improvement in motor function was not observed in patients whose motor symptoms were well controlled with levodopa.[98]

Anticholinergic or dopaminergic mechanisms may be responsible for TCA-induced improvement of some motor symptoms, including tremor and salivation.[97] The effects of TCAs on striatal dopamine activity, however, are complex and poorly understood.[99-101] One study found an increase in striatal dopamine level in rats following intraperitoneal injection of TCAs.[100] In contrast, another study noted that rats injected with imipramine and sacrificed 6 hours later exhibited an increase in dopamine level in the pons, medulla and cerebellum, but a decrease in the striatum.[102] Other studies suggest that TCAs may inhibit the uptake of dopamine.[101]

A recent questionnaire of PSG investigators indicated that TCAs were chosen as first-line agents in 41% of cases of depression in patients with Parkinson's disease.[103] The most commonly used TCAs were amitriptyline (52%), nortriptyline (33%), doxepin (10%) and desipramine (5%). The two most frequent reasons for choosing TCAs over the newer SSRIs included better efficacy in treating sleep disturbances and greater physician experience with the older drugs.[103]

Selective Serotonin Reuptake Inhibitors and Atypical Antidepressants

Few reported studies have examined the clinical effects of SSRIs and atypical antidepressants in Parkinson's disease.

We evaluated the tolerability and efficacy of sertraline in treating depression in Parkinson's disease in an open-label study and found significant improvement in depression (BDI) scores, while

parkinsonian (Unified Parkinson's Disease Rating Scale) and energy level scores were unchanged.[104] Meara and Hobson[105] noted similar findings in another open-label trial of sertraline in depressed patients with Parkinson's disease, along with improved quality of life measures in patients who responded to drug therapy.

A 2-year open-label study evaluating the tolerability and efficacy of paroxetine found that 85% of depressed patients with Parkinson's disease experienced a reduction in depressive symptomatology.[106]

Another trial found that amfebutamone, an antidepressant with indirect dopamine agonist properties, significantly improved motor symptoms, including gait and akinesia. There was modest improvement in depression, perhaps because dosages were optimised to treat parkinsonian features rather than mood.[107]

Thus, while open-label studies suggest that SSRIs and amfebutamone are effective in treating depression in Parkinson's disease, double-blind studies are lacking.

Complications of Antidepressant Treatment

Exacerbation of Parkinsonian Symptoms: Several case reports suggest that SSRIs may cause extrapyramidal symptoms (EPS) and can worsen motor signs in individuals with Parkinson's disease.

In one report, a 39-year-old woman with bipolar affective disorder whose symptoms were controlled with haloperidol developed cogwheel rigidity, masked facies and akathisia 2 weeks after starting fluoxetine. Extrapyramidal symptoms resolved with discontinuation of fluoxetine.[108] In another case report, paroxetine, a phenylpiperidine derivative, was thought to be responsible for aggravating parkinsonism in a 35-year-old woman with early Parkinson's disease.[109] Medication was withdrawn over a 2-month period and parkinsonian signs improved. EPS were also noted in 5 of 28 non-parkinsonian patients treated with fluoxetine for major depression in dosages ranging from 20 to 60 mg/day.[110] Within 2 weeks following withdrawal of fluoxetine, parkinsonian features improved.

Richard et al.[3] conducted a retrospective chart review of 476 patients with Parkinson's disease, and identified 5 possible cases of SSRI-induced worsening of motor function. In all 5 cases there were alternative explanations for aggravation of motor symptoms. In 2 cases, discontinuation of previously used TCAs, rather than the addition of SSRIs, may have caused increased parkinsonian features. In another case, an antipsychotic was used in combination with an SSRI because of levodopa-induced psychosis, and parkinsonian symptoms improved when the antipsychotic was stopped. In the fourth case, parkinsonian symptoms worsened only when sertraline was used in higher than recommended dosages (600 mg/day). In the remaining case, fluoxetine use may have been responsible for increased tremor, but whether this represents a worsening of parkinsonian motor symptoms is unclear. Many medications are thought to induce tremor through nondopaminergic mechanisms [e.g. valproic acid (sodium valproate)]. It should also be noted that in any study population, some patients' clinical symptoms may worsen even when there is no identifiable cause.

Clinical trials in populations with Parkinson's disease have failed to identify worsening of parkinsonian features with use of SSRIs, although no controlled studies have been performed. An open-label study examining the efficacy of sertraline in treating depression in Parkinson's disease did not find a worsening of parkinsonian signs.[104] Montastruc et al.[111] found no change in rigidity or bradykinesia scores in 14 nondepressed patients with Parkinson's disease treated with fluoxetine for 1 month. A retrospective chart review of depressed patients with Parkinson's disease treated with fluoxetine identified no worsening of parkinsonism.[112]

It is therefore unclear whether SSRIs have an adverse effect on motor signs in Parkinson's disease. Almost half of the PSG investigators queried by Richard et al.[103] were concerned that SSRIs might contribute to motor dysfunction, and 37% reported at least 1 incident in which this may have occurred. If SSRIs do exacerbate motor symptoms

in Parkinson's disease, the exact mechanism of action is unknown. Hypotheses include drug interactions, as well as inhibition of dopaminergic activity in the extrapyramidal system by serotonin.[112]

The Serotonin Syndrome: A constellation of symptoms called the 'serotonin syndrome' can be caused by SSRIs, either alone or in combination with selegiline, and may be associated with enhanced stimulation of serotonin receptors in the brainstem and spinal cord.[113] Criteria for the diagnosis include at least 3 of the following: mental status changes, myoclonus, diaphoresis, hyperreflexia, tremor, diarrhoea, shivering, incoordination and fever.[113] Seizures, coma and death may also occur.[114] Although arterial hypertension has also been reported with the concomitant use of fluoxetine and selegiline,[115,116] it is unclear whether this is part of the serotonin syndrome.

The serotonin syndrome can be confused with the neuroleptic malignant syndrome (NMS). Symptoms of NMS include hyperthermia, rigidity and autonomic instability, and the syndrome is usually caused by use of a dopamine receptor antagonist or dopamine depletor. It can also occur when dopaminergic agents are discontinued. In contrast, the serotonin syndrome is usually caused by the use of a serotonergic agent, and temperature and creatine kinase values are altered to a lesser extent.[117]

The serotonin syndrome is treated by discontinuation of the offending medication, along with supportive measures. Symptoms usually resolve over hours to weeks. The usefulness of serotonin receptor antagonists such as methysergide and cyproheptadine and β-blockers such as propranolol remains to be clarified.[113]

The serotonin syndrome caused by the combination of selegiline and an antidepressant is uncommon. Laine et al.[118] evaluated the risk of interaction between selegiline and citalopram, an SSRI,[118] in a randomised, placebo-controlled trial of healthy individuals. Patients received either citalopram or placebo, followed by concomitant selegiline (10 mg/day) for several days. Safety analysis revealed no significant adverse events or pharmacokinetic interactions between the 2 groups. Comparison of plasma levels of noradrenaline (norepinephrine), adrenaline (epinephrine) and 3,4-dihydroxyphenylglycol (DHPG) and urinary levels of serotonin and 5-HIAA failed to identify subclinical interaction between selegiline and citalopram.

Two chart reviews of patients who received a combination of SSRIs and selegiline failed to note adverse effects which had not already been reported with each respective medication.[119,120] In a survey of PSG investigators, only 0.24% of 4568 patients treated with combination therapy reported symptoms which were thought to be consistent with the serotonin syndrome and only 0.04% experienced symptoms which were considered 'serious'.[121]

Current information indicates that serious interactions between selegiline and antidepressants are rare, and it is possible that some patients may be at risk because of individual variations in metabolic pathways.

Future Clinical Trials: The safety and efficacy of antidepressants in the treatment of depression in Parkinson's disease should be evaluated by double-blind prospective clinical trials. Such studies should use standardised clinical criteria and validated and widely used neuropsychiatric scales. Clinical evaluations should also include an assessment of motor signs and the incidence of the serotonin syndrome. Doses of antiparkinsonian medications should be held constant during these studies, and antidepressants should be studied at sufficient doses and over sufficient time to adequately evaluate their effects. Retrospective studies indicate that serious adverse effects due to the serotonin syndrome appear to be rare, and it seems reasonable not to exclude patients who are receiving selegiline at stable dosages of 10 mg/day or less.

3.2.2 Selegiline (Deprenyl)

The monoamine oxidase (MAO) inhibitors were the first effective antidepressants.[122] Selegiline was designed as a 'psychic energiser', comprised of an amphetamine moiety combined with an antidepressant-like compound.[123]

Although selegiline is a relatively selective MAO-B inhibitor at oral dosages of 10 mg/day or less, at higher dosages it becomes a nonselective MAO inhibitor. Antidepressant effects occur at dosages of 30 to 40 mg/day, probably due to inhibition of MAO-A.[124] Selective inhibition of MAO-A, but not MAO-B, has been shown to result in antidepressant-like effects in rats.[125] A double-blind placebo-controlled study evaluated the effect of selegiline in patients with primary depression. Depression was unchanged after 3 weeks at 10 mg/day, but significantly improved after 6 weeks at 30 mg/day.[126] Another study reported no significant effect at dosages of 20 mg/day administered for 3 weeks.[127]

At dosages of less than 10 mg/day, selegiline is generally not associated with hypertensive reactions when administered with tyramine or other monoamines.[128] However, at higher dosages, its use is subject to precautions that would apply to MAO-A inhibitors, including a tyramine-restricted diet and discontinuation of levodopa.[129]

3.2.3 Dopamine Agonists

Dopamine agonists have antidepressant effects in animal models of depression.[130] There is also clinical evidence that dopamine agonists such as bromocriptine and piribedil[131,132] may possess antidepressant properties in patients without Parkinson's disease.[133,134] One open-label trial of pergolide in 20 patients with refractory mood disorders (either unipolar or bipolar) found substantial improvements in mood, interest and energy in 11 of 20 patients when pergolide was added to maximally tolerated doses of antidepressants.[131]

Pramipexole, a non-ergot dopamine D_2/D_3 agonist, has been found to reduce the negative symptoms of schizophrenia when used as an adjunct to antipsychotics.[135] Two case reports have also documented an improvement of treatment-resistant bipolar depression with pramipexole use.[136]

Double-blind, prospective studies are needed to assess the role of dopamine agonists as antidepressant agents in patients with Parkinson's disease.

4. Conclusions

Depression is common in individuals with Parkinson's disease, and its treatment may improve a patient's quality of life. Physicians need to routinely evaluate patients for the presence of depression during clinical evaluations. Further validation of clinical rating scales for depression in Parkinson's disease is warranted. Population studies do not indicate that patients experience worsening of motor signs with use of SSRIs, and the 'serotonin syndrome', caused by the combination of SSRIs and selegiline, appears to be rare. Antidepressants appear to be effective in treating depression in Parkinson's disease, but prospective double-blind studies are needed to confirm this impression.

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