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Selective Serotonin Reuptake Inhibitors Effect on Motor Function in Subjects with Parkinson’s Disease and Depression

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Selective Serotonin Reuptake Inhibitors Effect on Motor Function in Subjects with Parkinson's Disease and Depression

**Abstract**
Depression associated with Parkinson's disease (PD) is very common and by some estimates, affects 40%-50% of that population. The majority of these patients are treated with a selective serotonin reuptake inhibitor (SSRI). However, extrapyramidal adverse reactions are a side-effect of this medication and by causing inhibition of the dopaminergic path way, these medications could potentially worsen PD as measured by the Unified Parkinson's Disease Rating Scale (UPDRS). Hypothesis was that SSRIs would cause a statistically significant increase in the motor part of the UPDRS. This is a systematic review of the literature. An exhaustive search concerning Parkinson's disease and SSRIs, with specific attention to motor aspect of the disease, was undertaken using four different search engines. Though randomized, double-blinded, placebo controlled studies were lacking, six articles met the criteria and were evaluated in this review. Results show that SSRIs, do not worsen the motor part of the UPDRS with statistical significance in the short term, but can cause increased tremor for a minority of the patients. SSRIs are relatively safe in this population but will exacerbate motor symptoms at a higher incidence than the general population. The SSRIs, sertraline and citalopram, appear to be the best tolerated. Increased awareness should be given to patients with Parkinson's disease being treated with a selective serotonin reuptake inhibitor to manage their depression.

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Selective Serotonin Reuptake Inhibitors Effect on Motor Function in Subjects with Parkinson’s Disease and Depression

Philip McKay

A Clinical Graduate Project Submitted to the Faculty of the
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Abstract

Depression associated with Parkinson’s disease (PD) is very common and by some estimates, affects 40%-50% of that population. The majority of these patients are treated with a selective serotonin reuptake inhibitor (SSRI). However, extrapyamidal adverse reactions are a side-effect of this medication and by causing inhibition of the dopaminergic pathway, these medications could potentially worsen PD as measured by the Unified Parkinson’s Disease Rating Scale (UPDRS). Hypothesis was that SSRIs would cause a statistically significant increase in the motor part of the UPDRS. This is a systematic review of the literature. An exhaustive search concerning Parkinson’s disease and SSRIs, with specific attention to motor aspect of the disease, was undertaken using four different search engines. Though randomized, double-blinded, placebo controlled studies were lacking, six articles met the criteria and were evaluated in this review. Results show that SSRIs, do not worsen the motor part of the UPDRS with statistical significance in the short term, but can cause increased tremor for a minority of the patients. SSRIs are relatively safe in this population but will exacerbate motor symptoms at a higher incidence than the general population. The SSRIs, sertraline and citalopram, appear to be the best tolerated. Increased awareness should be given to patients with Parkinson’s disease being treated with a selective serotonin reuptake inhibitor to manage their depression.

Keywords: Parkinson disease and Serotonin re-uptake inhibitor.
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To my parents: Thank you for helping me to succeed and your support through the uncertainty.

To the Arthurs: Thank you for all of your help and kindness. You never know how many friends/relatives you have until you own a beach house.
List of Tables

Table I: PICO Comparison of Articles

List of Abbreviations

PD.................................................................Parkinson’s Disease
UPDRS............................................................Unified Parkinson’s Disease Rating Scale
SSRI...............................................................Selective Serotonin Reuptake Inhibitor
TCA..............................................................Tricyclic Antidepressant
SD..............................................................Standard Deviation
PDQ 39.........................................................Parkinson’s Disease Questionnaire 39
DSM IV......................................................Diagnostic and Statistical Manual 4th edition
HDRS 17......................................................Hamilton Depression Rating Scale 17
MMSE..........................................................Mini Mental Status Exam
BDI.............................................................Beck’s Depression Inventory
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Introduction

Parkinsonism is a neurological disorder that can manifest with tremor, rigidity, postural instability, and hypokinesia. The most common form of Parkinsonism is idiopathic Parkinson’s disease, the full name of a disorder leading to the loss of dopaminergic cells in the pars compacta region of the substantia nigra without any known cause, which is typically referred to as Parkinson’s disease (PD). The illness was first described in 1817 by James Parkinson, an English surgeon, in “An Essay on the Shaking Palsy.” Parkinson’s disease is a neurodegenerative disorder that affects 1%-2 % of the population over the age of 60 in the United States.¹ This number is expected to increase with the growth of our aging population.

It has been estimated that 40% to 50% of patients with PD have co-existing depression.² The majority of these patients are treated with a selective serotonin reuptake inhibitor, SSRI, because of the more desirable side effect profile. However, there have been questions as to whether these medications possibly worsen the symptoms of PD. Over 100 detailed reports have been published regarding SSRIs exacerbating PD motor function in the last decade.²¹ Tremor and extrapyramidal symptoms are a known adverse reaction of SSRI medication. Medication induced movement disorders are a differential diagnosis when considering a diagnosis of PD. The conflicting literature, accepted practice, and lack of strong data with regard to using an SSRI in treating depression in PD, is what prompted this systematic review. The balance and interaction of neurotransmitters is poorly understood. Could treating patients who have Parkinson’s disease with a selective serotonin reuptake inhibitor worsen the disease?

The classic cardinal features of PD include resting tremor, rigidity, bradykinesia, and gait disturbance/postural instability. Associated features are masked fascies, micrographia, decreased
blinking, freezing, and flexed posture. Non-motor features are becoming increasingly important to the 
health of the patient and include mood disorders (anxiety and depression), sleep impairment, and 
dementia. Not all patients will manifest all of these features and, diagnosing the disease is challenge to 
most physicians, but an accurate diagnosis can be made about 90% of the time if a person is followed 
by a movement disorder specialist.\textsuperscript{3}

Differential diagnosis for PD is large, as there are many diseases that can manifest with Parkinsonism and these must be excluded for proper management. A partial list of the differential 
includes: dementia with lewy bodies, multiple system atrophy, corticobasal degeneration, 
spinocerabellar ataxias, essential tremor, and progressive supranuclear palsy. Secondary causes of 
Parkinsonism include: toxins, head trauma, neoplasm, metabolic disorders, small vessel disease, and 
drugs or medications. The latter being the most common form of secondary Parkinsonism is usually 
reversible on withdrawal of the offending agent, this is not always the case.\textsuperscript{3}

The diagnosis is made by clinical observation of the signs and symptoms with which the patient 
presents. There are no physiological tests that would be pathopneumonic, and imaging is usually 
unrevealing.\textsuperscript{3} Clinicians usually make a diagnosis on two out of the three classic signs, tremor, 
bradykinesia, or rigidity, and a favorable response to dopamine. However, many patients with 
Parkinsonism can respond favorably to a dopamine challenge and some patients with PD will not 
respond, thereby making reliance on this unwise. Though pathologically the loss of dopaminergic 
neurons in the substantia nigra and proteinaceous inclusions called Lewy bodies are what define this 
disease, other pathology is coming to light as typical of the disease, that includes dysfunction in 
serotonin (midline raphe), norepinephrine (locus coeruelus), and cholinergic (nucleus basilis of 
meinert) neurons, as well as other neurons throughout the CNS.\textsuperscript{1}

The exact cause of PD is not known, but like many neurological disorders, a genetic 
susceptibility along with certain environmental factors is thought to be likely. Many genetic mutations 
have now been demonstrated in patients with Parkinson’s and includes the genes, alpha-synuclein,
UCH-L1, DJ-1, PINK, LRRK2, and the protein Parkin. The exact cause of cell death is unknown and that is the focus of research. Genes are thought to play more of a role when the patient develops Parkinson’s before the age of 50.¹

The depression associated with PD will lead to feelings of sadness and helplessness as in other conditions, but the incidence of depression in PD is higher than in the general population and that experienced with most other chronic degenerative diseases.¹ ⁴ That being said, the severity of depression in most of these patients is mild to moderate, with about 4%-22% having more profound depression.⁵ Depression is associated with increased disease severity, and decreased quality of life. It is unknown if the depression in PD is due to having a progressive disease, or due to the monoamine disregulation, or both. Evidence of the depression being caused by dopaminergic, serotonergic, or noradrenergic disregulation is provided by the early appearance of depressive symptoms, often before clinical signs of motor dysfunction are present.

Depression in PD is thought to be under-recognized and under-diagnosed. Many patients will get some relief with dopamine replacement, but this usually happens slowly, so dopamine deficiency is not thought to be the only cause.⁶ It is recommended that patients with PD and mild depression, be treated first with a dopamine agonist, as dopamine has been shown to decrease depressive symptoms.¹ Signs of depression often pre-date the physical signs of the disease, and often occur in conjunction with an increased off-state, so treatment of the motor symptoms may help with the depression. In patients with persistent feeling of sadness, who have made lifestyle adjustments and are optimized on PD medication, it is recommended that antidepressant be used, and most commonly these medications are SSRIs.

Selective serotonin reuptake inhibitors are considered to have a more desirable side-effect profile when compared to tri-cyclic antidepressants (TCAs), which through their anti-cholinergic effect can worsen cognitive function. SSRIs are thought to have equal efficacy in treating depression as TCAs, given an adequate amount of time in the blood stream. However, a recent double blinded
randomized trial did show that SSRIs were no different from a placebo in treating depression.\textsuperscript{7} In an older study that surveyed a group of 71 neurologists, 43\% were concerned that SSRIs could potentially worsen motor function and 37\% felt that they had seen this in practice at least once. Nevertheless, 51\% of these clinicians used SSRIs as first line therapy for depression in Parkinson’s disease, feeling that the benefits outweighed the risk.\textsuperscript{8}

SSRIs have been linked to extrapyramidal symptoms. The exact mechanism is unknown, but it has been suggested that serotonin may have an inhibitory mechanism of action on the dopaminergic system.\textsuperscript{9} Risk factors for the development of EPS with SSRI medication include PD.\textsuperscript{10} SSRIs have a flat dose response curve meaning that once optimal levels are achieved increasing the dose will yield more side effects without more antidepressant effect. Not all SSRIs have the same molecular structure and, as a consequence, have different half lives and are metabolized differently. However, due to the paucity of studies on PD and SSRIs in the literature, it was impossible to perform a valid systematic review on a particular SSRI. All of the SSRIs have been used in the treatment of depression in Parkinson’s disease and so the focus of this study included all Selective serotonin reuptake inhibitors.

Anticholenerics are used to treat the motor dysfunction in patients with PD. Tricyclic antidepressants could potentially be useful for these patients, but TCAs block central and peripheral cholinergic receptors leading potentially to dry mouth, blurred vision, urinary hesitation and retention, cognitive symptoms and tachycardia. They can stimulate histamine and adrenergic receptors leading to sedation, weight gain, and orthostatic hypotension. Many other medications can be used in the treatment of depression in Parkinson’s disease including effexor, nafazodone, trazadone, wellbutrin, Remeron.\textsuperscript{6}

The Unified Parkinson’s Disease Rating Scale (UPDRS) is a tool used to follow the progressive course of PD. A total of 199 points considered in six different categories. Each category contains a number of sub sections. Sections one for example assesses mentation, behavior, and mood. Sections two and six look at daily living activities from different standpoints. Section three examines motor
symptoms and this represents the main focus of this review, with the remaining two sections addressing complications of therapy and modified Hoehn and Yahr staging. The lower the patients score the better the prognosis. A zero on this scale which is the most widely used system for evaluating the progress of PD, would represent no sign of PD while a score of 199 would indicate the most advanced form of the disease.

The Hoehn and Yahr scale allows for a quick broad rating of the disease and though relevant for classifying the disease, was not thought as comprehensive at monitoring Parkinson disability in the short term as the UPDRS. The scale, from one to five, classifies patients with minimal functional disability and unilateral limb involvement, stage one, and progresses to patients that are bed or wheelchair confined, stage five.

The purpose of the study was to evaluate if SSRIs exacerbated the symptoms of PD with respect to the motor part of the UPDRS. There are many different signs and symptoms of PD, but the motor aspects are a major marker for its progression and a determination of treatment success. A literature search presented conflicting data and with the number of Parkinson’s disease patients using an SSRI to treat their depression it was considered important to assess the risk of further harm.

Hypothesis of the study was that SSRIs would cause a statistically significant exacerbation of motor symptoms by increasing serotonin which would inhibit dopamine and thereby cause an increase in the motor part of UPDRS. Significance of a systematic review is potentially second only to a meta-analysis in its clinical application.

**Methods**

This is a systematic review of the literature. To locate a representative set of citable scientific papers, an exhaustive literature search was done using four different search engines, including: Medline, Cinahl, Pubmed, and Psychinfo. Search terms used in Medline included serotonin reuptake inhibitor (24949) and Parkinson disease (34712). Using the term “and,” these terms were then combined (120). They were limited to English language and trials involving only humans (94). All of
these results were then searched for relevant articles. Next the individual SSRIs, fluoxetine, citalopram, sertraline, fluvoxamine and paroxetine were combined with Parkinson disease to see if any articles were missed, this was only done with Medline. Parkinson disease and SSRI were searched and combined in Psychinfo which yielded 14 results, Cinahl yielded nine results, and Pubmed yielded 182 results.

All results were screened by the abstract and, whenever the study looked at subjects with PD and treatment with an SSRI, this was read. If the abstract showed that the study was similar to the objective, then the article was read. Articles were then evaluated for relevancy to the question and evaluated for applicability.

UPDRS part III as either primary or secondary objective in a study was the primary inclusion and exclusion criteria. Since the motor aspect of the disease was being evaluated, it was felt that if patients were taking other medication, especially Parkinson’s medication, it was essential that this medication remain stable. Studies that did not address the issue of keeping Parkinson’s medication stable throughout the trial were excluded.

The materials, methods, and outcomes of the selected studies were critically evaluated and compared in an effort to perform a systematic review. Depression indices and other relevant outcomes of the studies, though not the primary purpose of this systematic review are included for discussion purposes.

Results

After a systematic search of the literature it was obvious that large, placebo controlled studies meeting the criteria were lacking. Efforts were made to include all relevant articles. Below are the six articles that met the criteria.

The article, by Silvia Marino et al 11, compared the effect of liquid and oral sertraline over a period of six months on 54 patients with PD and depression. This study monitored depression, mini-mental status exam, and UPDRS. This was an open-label study which randomly assigned the 54
patients to each group where they received 50-200 mg/day sertraline. All subjects started on 50 mg/day and titrated up according to investigator judgment. Each visit was carried out by the same investigator who was not blind to treatment.

The article met the criteria by involving patients with PD and depression who were treated with liquid oral concentrate and tablet sertraline, a selective serotonin reuptake inhibitor. No change in Parkinson’s medication, levodopa or dopamine agonist was allowed four months proceeding or during the trial.

Results of the study showed UPDRS did not change significantly over the six month period. Four patients dropped out of the trial in the first month, two due to nausea with the liquid form and two due to “weakness” with the tablet form. Depression markers as measured by the Turkish version of the Hamilton Depression Rating Scale (HDRS) and Turkish version of the Montgomery and Asberg Depression Rating Scale improved with statistical significance.

The Clinical Global Impression-Severity of Illness Scale and The Clinical Global Impression–Global Improvement Scale improved with statistical significance at all visits. The Parkinson’s disease questionnaire (PDQ-39) significantly improved with respect to mobility, activities of daily living, emotional, and stigma scales. Mini mental status exam (MMSE) remained unchanged throughout the study.

Statistical analysis was done at baseline and correlated with the final visit using nonparametric Spearman rank order correlation. Values were considered significant at the 0.5 level. All patients were diagnosed with depression according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM IV). At baseline, the mean age of the patients in the two groups was 63.7 (standard deviation 9.5) years, no mention was made of how long subjects had PD, the mean Hoehn and Yahr stage was 1.8 (SD 0.5), and the mean UPDRS motor sub score was 22.1 (SD 7.9). Subjects were monitored for UPDRS scores as a primary objective along with depression. Patient’s had to
show signs of motor stability with regard to their PD for at least 3 months. In addition, ten patients were affected by Parkinson’s in the advanced stage and demonstrated swallowing problems.

The article, by Angelo Antonini et al¹², compares amitriptyline and sertraline in patients with PD and depression. The study measured Hamilton depression rating scale 17 (HDRS-17), MMSE, and UPDRS on a total of 31 subjects. The sertraline subgroup consisted of 16 subjects, while the amitriptyline subgroups consisted of 15 subjects. This was a prospective, investigator blinded, randomized study to compare an SSRI to a TCA. Sertraline was started at 25 mg/day and titrated up to 50 mg/day. Clinical and neuropsychological evaluations were carried out by a neurologists and neuropsychologist blinded to treatment. Only patients with stable motor functions over the past three months were included in the study.

The article met the criteria by involving subjects with PD and depression. All patients were diagnosed with PD according to the United Kingdom Parkinson’s Disease Society Brain Bank and depression according to the DSM IV. Five subjects were taking levodopa alone and the remaining were taking levodopa combined with dopamine agonist. In addition, six subjects were taking amantadine and three subjects were taking entacapone for the treatment of PD. No change in Parkinson’s medication was allowed three months before and during the three month study.

Results showed that UPDRS III did not change significantly over the three month study period for either group. There were 12 patients left in the sertraline group after four subjects prematurely dropped out within the first month, this was due to: nausea (2), confusion (1), and hypotension (1). Four subjects also dropped out of the TCA group for confusion and visual hallucination (2), sleepiness (1), and headache and tachycardia (1). MMSE in both groups did not change with statistical significance. HDRS-17 significantly improved in both the SSRI and TCA groups. PDQ-39 with regard to mobility, activities of daily living, emotional, and stigma scale significantly improved in the SSRI group only.
Statistical analysis was performed using analysis of variance repeated measures with Bonferroni correction for multiple comparisons. Values were considered significant at the 0.5 level. At baseline, the mean age of the patients in the SSRI group was 71.8 (standard deviation 6.5), median time with the diagnosis of PD for 7.5 years (SD 3.4), and median Hoehn and Yahr stage was 2.0 (SD 0.7). UPDRS and depression indices were the primary outcomes in this trial.

The article, by Asuncion Avila et al., compares nefazodone, a serotonin 2 antagonist/reuptake inhibitor to the SSRI, fluoxetine, in depressed patients with PD. The study measured Beck Depression Inventory (BDI), UPDRS parts II and III, modified Hoehn and Yahr Staging, Schwab-England Activities of Daily Living Scale, and Abnormal Involuntary Movements Scale on a total of 16 subjects. There were seven subjects assigned to the fluoxetine group and nine assigned to the nefazodone group. This was a pilot single-blinded randomized study.

The article consisted of subjects with idiopathic Parkinson’s disease and depression. They diagnosed depression according to the DSM IV. The dopaminergic treatment remained unchanged four weeks prior and throughout the treatment, 14 patients were on levodopa-carbidopa and two were taking dopamine agonist alone. Patients were evaluated at baseline, 15\textsuperscript{th}, 30\textsuperscript{th}, 60\textsuperscript{th}, and 90\textsuperscript{th} day after the inclusion in the study, by a neurologist who remained blinded to the treatment. Fluoxetine was started at 10 mg/day and then increased up to 20-50 mg/day. The dose could be reduced if side-effects occurred.

Results show that neither UPDRS part II or part III changed significantly for patients in the SSRI group. There was modest improvement in the nefazodone group. There were a total of seven patients in the fluoxetine subgroup and no subjects dropped out. Three dropped out of the nefazodone group, two for worsened tremor and one for diarrhea. The BDI scores improved significantly from baseline to final visit for both groups, with no difference between groups. The modified Hoehn and Yahr staging, the Abnormal Involuntary Movements scale, and the Schwab-England Activities of Daily Living Scale remained unchanged throughout the study in both treatment groups.
Statistical analysis using repeated measures ANOVA was applied to UPDRS and BDI scores on all visits. A bivariate analysis was initially applied to differences between groups and considered significant if less than 0.05, there was no statistical difference between groups initially. At baseline, the mean age was around 70.4 years (SD 6.4), median time with the diagnosis of PD was 60 months (range 4-168 months), median UPDRS motor part was 32 (SD 7.4), and the median Hoehn and Yahr stage was 2.6 (SD 0.8). The primary objectives were depression and UPDRS.

The article, by Liborio Rampello et al 13, compares subjects with PD and depression to those without depression. Both groups were given citalopram and half of the non-depressed subgroup was given a placebo. They measured UPDRS III, the Beck Depression Inventory (BDI), and the Hamilton Depression Rating Scale (HDRS) on a total of 46 patients to evaluate motor and non-motor symptoms in an open label controlled trial. There were 18 subjects in the depressed subgroup and 28 in the non-depressed subgroup.

The article involved subjects with PD and half of the subjects had depression. The diagnosis of PD was made when patients demonstrated two of the three cardinal signs, bradykinesia, rigidity, and resting tremor. Diagnosis of depression was made by a psychiatrist according to the DSM IV. All patients were receiving levodopa plus carbidopa and no change was made in this medication. Patients on dopamine agonist or with motor fluctuations were not included. No change in PD medication was allowed during the trial.

Citalopram, was started at 10 mg/day and then increased to 20 mg/day after one week, was given in an un-blinded manner to all patients with depression and 14 of the 28 without the diagnosis of depression, the rest were given a placebo. UPDRS III was evaluated at baseline, one, and four months of treatment by the same blinded examiner.

Treatment in the depressed subgroup did improve UPDRS with statistical significance, specifically with regard to bradykinesia and fingertaps, defined in the study as part 23 and 31 of the UPDRS part III sub scores. A total of 44 subjects completed the trial. Two in the depressed subgroup
did not complete the study because of residence change and poor compliance. The BDI and HDRS both improved with statistical significance for the depressed subgroup.

Statistical evaluation was made by analysis of variance for repeated measures. At baseline, mean age was 64 years (SD 5.3), median time with diagnosis of PD was 6.4 years (SD 3.2), and median Hoehn and Yahr stage was 2.8 (SD 1.2). Primary outcome of the study was UPDRS III and the depression indices.

The article, by Dell’Angello et al 14, compares four different SSRIs in the treatment of depression in patients with PD. They used citalopram, fluoxetine, fluvoxamine, and sertraline in 62 patients in an open label prospective manner for six months and monitored UPDRS II and III scores, BDI, and HDRS.

UPDRS scores did not change significantly for any of the groups, but aggravation of tremor was seen in a total of four patients, two with fluvoxamine and two with fluoxetine. This resolved shortly after discontinuation of said medications. A total of 52 patients completed the study. Three drop outs also occurred with citalopram and sertraline for poor compliance and dysphoria. Minor side effects were anxiety, dizziness, nausea, and parasthesia. The depression indices both improved with statistical significance for all of the medications used in the study.

The article consisted of subjects with PD and depression. The diagnosis of depression was new in all patients and was made according to the DSM IV. All patients were on levodopa and 40 of 62 were on dopamine agonist. No change in these medications was allowed to take place during the six month study. Previous TCAs were withdrawn at least one month prior to the study. Evaluations were performed by a physician blinded to treatment and without knowing the subjects previous score at baseline, one, three, and six months.

Statistical analysis was made by analysis of variance for repeated measures. At baseline, the mean age of the subjects was 62.9 years (standard deviation 5.3), median duration of PD was 54.8
months (SD 7.6), and median Hoehn-Yahr stage was 2.2 (SD 0.4). Primary outcome was specifically to monitor motor function and looked at four different SSRIs on a total of 62 patients.

The article by Cervalo et al\textsuperscript{15}, looked at the effect that paroxetine had on motor and depressive symptoms in 33 non-demented, depressed patients with PD in an un-blinded, prospective study. The investigators monitored Unified Parkinson’s Disease Rating Scale part III, Beck Depression Inventory and Hamilton Depression Rating Scale.

The study consisted of subjects with PD and depression. Diagnosis of depression was made according to DSM IV. All patients were on levodopa therapy and 18 on dopamine agonist. No change in these medications was allowed during the trial. Paroxetine was added starting at five mg/day and increased gradually up to two mg/day. Parkinson’s symptoms were evaluated by the UPDRS III at baseline, one, three, and six months of therapy and each new assessment was performed by the same un-blinded examiner.

UPDRS did not change significantly. Four subjects dropped out for poor compliance, lack of antidepressant efficacy, and two for visual hallucinations. One individual completed the study, but experienced worsening of tremor which returned to baseline after two months. Side effects included dizziness, paraesthesia, anxiety, nausea, and palpitation. The depression indices of BDI and HDRS improved with statistical significance once again.

Statistical evaluation was made by analysis of variance. At baseline, the mean age of the subjects was 63.3 years (standard deviation 2.8), the median duration of PD was 52.2 months (SD 8.1), and median Hoehn and Yahr stage was 2.1 (SD 0.3). The primary outcome of the trial was UPDRS and depression indices.

**Discussion**

In an attempt to answer this question with the dearth of material available in the literature, homogeneity and study quality suffered. All trials consisted of prospective studies, some looked at UPDRS as primary outcomes, and others as secondary outcomes.
Several good articles were not included in the study due to the fact that the Parkinson’s medication was not mentioned\textsuperscript{16} and no statement was made indicating that the medication remained constant. \textsuperscript{17} Another reason that studies were excluded was a failure to measure UPDRS before and after. \textsuperscript{18,19,20}

One study looked at a French pharmacovigilance database to analyze extrapyramidal adverse drug reactions reported in patients with PD using an antidepressant and then compared different classes of antidepressants.\textsuperscript{21} Their conclusion was that there was no significance difference, but it is well known that adverse drug reactions are notoriously under-reported.

PHARMO database studies were not included. There were two relevant studies that compared increasing Parkinson’s medication in response to treatment with either SSRI or TCA treatment.\textsuperscript{22,23} This approach could have been another way of looking at the question and they did reach different conclusions. Too many unknown variables are inherent in this type of study, such as, individual physician prescribing practices. It is also possible that worsening of PD occurred without an increase in medications, and also unknown was whether the patients in the TCA group actually had depression, as these medications can also be used to treat other disorders.

Several recent studies were done that looked at SSRIs in the treatment of depression which were double blinded, randomized, and placebo controlled, but they didn’t address motor aspects of PD.\textsuperscript{24,7}

Case study reports of SSRI induced movement disorders have been in the literature for many years. They demonstrate much like the six studies included, that certain people will exhibit a worsening in Parkinson’s disability shortly after starting an SSRI. A study was done in 1996 that looked at the incidence of extrapyramidal effects with SSRIs and they concluded that side-effects are infrequent, but clinicians should be aware of them.\textsuperscript{9} A study was done in 1993 that looked at four cases specifically of fluoxetine exacerbating Parkinson’s disease.\textsuperscript{25} A study was also done on two cases of fluvoxamine\textsuperscript{26} and paroxetine\textsuperscript{27} worsening PD. The case studies though providing evidence to
support the hypothesis were excluded based upon low validity and not being homogenous with the other studies.

Fluoxetine, fluvoxamine, and paroxetine worsened tremor in a total of five subjects in the Dell’Angelo\textsuperscript{14} and Cervalo\textsuperscript{15} studies. These medications are known to have longer half lives as opposed to some of the other medications in the SSRI class. Citalopram improved UPDRS in the Rampello\textsuperscript{28} study. However, in this study the same evaluator, although blinded to treatment, evaluated the same subjects on each visit. In the Dell’Angello study, which also used citalopram, they demonstrated no change in UPDRS after treatment. Citalopram as opposed to fluoxetine, paroxetine and fluvoxamine, is said not inhibit the cytochrome P450 isoenzyme and it is reported that there is no interaction between levodopa and citalopram.\textsuperscript{28}

Though no worsening of PD was shown with statistical significance, motor exacerbation did occur shortly after starting an SSRI in about 3\% of the subjects. In these subjects, the motor part of the Unified Parkinson’s Disease Rating Scale returned to baseline soon after discontinuing the medication. Adverse drug reactions consisting of worsened motor dysfunction does appear rather infrequent and seems to occur with SSRIs with longer half lives. However, though these medications are thought to be well tolerated, side effects caused over 13\% of these subjects to terminate the trial early.

A total of 24 out of 190 subjects with the diagnosis of Parkinson’s disease and depression treated with an SSRI prematurely terminated these studies early. This was due to the following adverse reactions: irritability, poor compliance, sedation, lack of antidepressant efficacy, confusion, hypotension, weakness, and visual hallucinations. In the patients that remained, minor side effects ranged from anxiety and nausea to palpitations and dizziness.

In the general non-Parkinsonian patient the incidence of extrapyramidal symptoms with SSRI medications is unknown,\textsuperscript{29} but have been estimated to be one to two case per 1,000 treated patients.\textsuperscript{21} It does appear that patients with Parkinson’s disease are at a higher risk for developing these symptoms.
than the general population. Monitoring a patient on these medications is essential, especially after initiating treatment.

It is interesting to note that the two studies that included Parkinson’s disease questionnaire 39 as part of the evaluation there was a significant improvement in patient perception of motor ability after treatment, even though UPDRS part III remained unchanged. The SSRI sertraline, in the Marino\textsuperscript{11} and Antonini\textsuperscript{12} study, improved PDQ 39 with statistical significance. This raises more questions, demonstrates the importance of treating depression, but also suggests how strong the placebo effect can be in this population.

Recommendations for future trials would be to involve as many subjects as possible, double blindered, placebo controlled, and randomized studies. It is also imperative to study the long term consequences that these medications have on an individual with PD.

**Limitations of study**

This systematic review is limited by the availability of relevant literature with regard to SSRIs and PD. It is further limited by studies that effectively evaluate motor component of the Unified Parkinson’s Disease Rating Scale. The number of subjects monitored in these studies was minimal and making conclusions with relative certainty is difficult when the statistical power of each study is so small. The short time frames of these trials are not ideally suited for analyzing the effect antidepressant may have on these subjects.

In the Marino article\textsuperscript{11} two subjects dropped out due to “weakness.” The weakness was not described further and could have potentially involved motor dysfunction. The study is limited by the open label design, small number of subjects, having no placebo to measure the experimental groups against, and the same un-blinded investigator evaluated the patients on each visit. The Antonini study\textsuperscript{12} consisted of only 12 subjects in the SSRI group. This study was open label and lasted only three months. The Avila study,\textsuperscript{2} was open label and consisted of only seven subjects in the SSRI group. Furthermore, the dose of the investigational medication could be reduced if side effects occurred. In
the Rampello study,\textsuperscript{13} the same blinded examiner evaluated subjects on only 3 visits, the small number of subjects, and open label design limit this study further. The Dell’Angelo study\textsuperscript{14} is limited by the open-label design and no placebo as a control. The Cervalo study,\textsuperscript{15} was also an open label design which included no comparison or placebo group to measure the experimental group against.

PD is a progressive disorder, which makes evaluating any aspect that could potentially worsen the disease difficult. It would seem that in a disorder such as this, it is imperative to have a placebo group to evaluate against the experimental group. This systematic review of the literature looked at different SSRI medications which have varied structure, half lives, and therefore metabolism.\textsuperscript{15} It would have been ideal to perform a systematic review on only one particular SSRI medication. Double blinded, randomized, placebo controlled studies that evaluated a large number of patients and monitored the effect SSRI medications had on the motor component of PD were not available.

\textbf{Conclusions}

Treating depression is vital for an improved quality of life in patients with Parkinson’s disease and may have a positive effect on the patient’s own perception of their motor dysfunction, even without objective improvement seen in the motor part of the UPDRS. Selective serotonin reuptake inhibitors did improve the depression indices with statistical significance in all of these studies.

Though safe for the majority of patients, those with Parkinson’s disease and depression are at an increased risk of motor dysfunction after treatment with an SSRI than the general population. The SSRIs, citalopram and sertraline, appear to be the safest medications for treating depression in patients with Parkinson’s disease.

The effect that selective serotonin reuptake inhibitors have on the progression of Parkinson’s disease in the long term is unknown. Whether SSRIIs are synergistic or antagonistic with regard to dopamine is still unknown. The modulation of dopamine by serotonin is still poorly understood and complex, more work needs to be done with regard to how these neurotransmitters interact with each other.


3. Chou K. Diagnosis of Parkinson disease. Available at: [http://www.uptodate.com/online/content/topic.do?topicKey=move_dis/7776&selectedTitle=1~150&source=search_result](http://www.uptodate.com/online/content/topic.do?topicKey=move_dis/7776&selectedTitle=1~150&source=search_result).


<table>
<thead>
<tr>
<th>Author/Date</th>
<th>Study type</th>
<th>Population/ #depressed pts that received SSRI (# lost)</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marino, Silvia et al/ 2008</td>
<td>Open label prospective study</td>
<td>PD with depression/ 54 pts (4 lost)</td>
<td>Sertraline</td>
<td>None</td>
<td>No significant difference UPDRS at 0, 2, 4 and 6 months</td>
</tr>
<tr>
<td>Antonini, Angelo et al/ 2008</td>
<td>Open label prospective study</td>
<td>PD with depression/ 16 pts (4 lost)</td>
<td>Sertraline</td>
<td>Amytriptiline</td>
<td>No significant difference UPDRS at 0, 1, and 3 months</td>
</tr>
<tr>
<td>Avila, Asuncion et al/ 2003</td>
<td>Open label prospective study</td>
<td>PD with depression/ 7 pts (0 lost)</td>
<td>Nefazodone</td>
<td>Fluoxetine</td>
<td>No significant difference UPDRS at 0, visit 1, 2, 3, and 4</td>
</tr>
<tr>
<td>Rampello, Liborio et al./ 2002</td>
<td>Open label prospective study</td>
<td>PD with depression/ 18 pts (2 lost)</td>
<td>Citalopram</td>
<td>Placebo</td>
<td>Improved UPDRS at visit 0, 1, and 4 months</td>
</tr>
<tr>
<td>Dell’Angelo, Grazia et al/ 2001</td>
<td>Open label prospective study</td>
<td>PD with depression/ 62 pts (10 lost)</td>
<td>Citalopram Fluoxetine Fluvoxamine Sertraline</td>
<td>None</td>
<td>4 w/ inc. tremor UPDRS at 0, 1, 2, and 4 months no significant difference</td>
</tr>
<tr>
<td>Cervolo, R. et al/ 2000</td>
<td>Open label prospective study</td>
<td>PD with depression/ 33 pts (4 lost)</td>
<td>Paroxetine</td>
<td>None</td>
<td>1w/ inc. tremor UPDRS at 0, 1, 3 and 6 months no significant difference</td>
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