THE EFFECTS OF ANTIDEPRESSANTS ON THE HEALTH OUTCOMES OF PARKINSON'S DISEASE PATIENTS: A META-ANALYSIS

by

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Abstract

THE EFFECTS OF ANTIDEPRESSANTS ON THE HEALTH OUTCOMES OF PARKINSON'S DISEASE PATIENTS: A META-ANALYSIS

by

Pasquale Frisina

Adviser: Joan C. Borod, Ph.D.

A meta-analysis of 44 placebo-controlled trials was conducted to examine three issues pertaining to the safety and efficacy of antidepressants in Parkinson's disease (PD). The first examined the magnitude and significance of the effects of antidepressants on depression. The second assessed whether or not antidepressants can provide salutary benefits to PD patients. Finally, the third issue was concerned with the side effect profile of antidepressants. To examine these three issues, a meta-analysis was conducted using Cohen's *d* as the effect size. The results show that TCAs produced a moderate antidepressant effect ($d = .55$, $p = .01$). TCAs also provided salutary benefits on motor outcomes ($d = .30$, $p = .07$), headache pain ($d = 1.79$, $p = .00$), and global psychological function ($d = .81$, $p = .00$). Although a significant effect size result was observed on adverse events ($d = -.27$, $p = .02$), they were deemed tolerable because PD patients subjectively evaluated their TCA medication positively ($d = 1.02$, $p = .01$). SSRIs produced a robust antidepressant effect on moderately depressed PD patients ($d = .44$, $p < .05$). A modestly positive and significant effect size result was observed with SSRIs on motor function ($d = .34$, $p < .05$), and there were no significant side effects ($d = -.002$, $p =$

.50). These results provide evidence that SSRIs can be used to treat depression without the fear of worsening PD. Finally, selegeline did not improve depression when given at a dose where it was influencing dopamine metabolism (i.e., 10 mg daily). However, the MAO-B inhibitor did improve motor function (d = .36, p < .00), global psychological functioning (d = .21, p <.00), and health-related quality of life (d = .23, p <.00**).** Few effects were observed with selegeline (d = -*.07*, *ns*), especially with mortality (d= -.06, p = .10) and depression (d= .15, p = .06). All things considered, the decision to choose between antidepressant classes should be carefully considered and monitored on an individual basis, weighing (and/or ranking) the benefits of improving depressive symptomatology together with the risk of creating and tolerating side effects.

DEDICATION

I would like to dedicate this project to the very special people in my life. The first is my wife, Charlene Frisina. Her love and devotion served as a buffering agent against the daily hassles and constraints of graduate life. Only she really knows at what expense it took to complete this entire process. I also dedicate this project to my son, Nunzio. His presence in my life had made the completion of this project a more imperative goal than my own needs.

I also want to dedicate this project to my grandparents, Rose and Pasquale Friello. My grandmother's affliction and battle with Parkinson's disease brought this project to life. This project would have not been possible if it was not for her active and loving participation in my life. I can only hope that this project will reward her sacrifices by improving the quality of life for the many people that are suffering just like her. To my grandfather, you have taught me that it is always important to approach life with a sense of calm and optimism.

Finally, I dedicate this project to Saint Mary and Saint Anthony. They have always provided me with the peace that I needed during difficult times. I will always be encouraged by the efficacy of their intercession.

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I am also grateful to my other committee members. Harriet Tenenbaum's experience with the meta-analytic technique was invaluable during the data acquisition, analysis, and interpretation stages of this research process. I will always be thankful to her because she has acted as both a friend and mentor during the last stages of my graduate education. I am also grateful for Nancy Foldi's contributions to this project. Her in-depth knowledge of clinical neuropsychology has helped refined this project into something that is worthy of sharing with the rest of the academic and scientific community. Laura Rabin and Chris Morrison were devoted readers on this project. Their individual contributions have added greatly to the quality of this work.

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Introduction

Parkinson's disease (PD) is a neurological disorder which disrupts the nigrostriatal pathway to produce tremor, bradykinesia, rigidity, and postural abnormalities. While PD is generally characterized as a movement disorder, depression occurs frequently in this neurological population (Edwards et al., 2002). It is has been estimated that roughly half of all PD patients suffer with depression (Doonief et al., 1992; Raskin, Borod, & Tweedy, 1990). Although the etiological factors that contribute to depression are still unclear, it is certain that many PD patients are left untreated to cope with the negative emotional affect that they are experiencing. Specifically, it has been estimated that only 20% of all depressed PD patients receive any treatment for their psychological health (Huber, Paulson, & Shuttleworth, 1988; Mayeux et al., 1986; Starkstein et al., 1990). Regrettably, if depression is left untreated, there is an increased risk for developing greater physical disability and reduced quality of life (Edwards et al., 2002). Thus, the question remains as to why the treatment of depression has received such little attention from the medical community in spite of being a risk factor for poorer health in PD.

One explanation for why depression has been overlooked in the treatment of PD is partly due to the patient's overshadowing concern for their physical as opposed to their psychological health. Brod, Mendelsohn, and Roberts (1988) have provided some evidence for this notion by observing that only 11% of depressed PD patients rated their psychological condition as a concerning health problem. Similarly, it was observed in another study that depression failed to rank as one of the 20 most bothersome symptoms experienced by depressed PD patients (Scott, Borgman, Engler, Johnels, & Aquilonius,

2000). Thus, it can be inferred from these studies that even when PD patients are suffering from affective disturbances, they are not likely to complain about it to their physicians. Therefore, it is essential that physicians regularly screen for depression when treating their PD patient, so that patients do not have to experience affective disturbances for a prolonged period of time. However, it should be added that it is often difficult to diagnose depression in this clinical population because many of the cognitive (e.g., decreased concentration), motor (e.g., agitation), and somatic (e.g., decreased energy and disturbed sleep) features of PD and depression overlap (Edwards et al., 2002).

The issue of treatment is also complicated by the lack of reliable and valid measurements for depression in PD. More specifically, the research has shown that the incidence of depression in PD tends to vary depending upon which tools are used to measure depressive symptoms. For instance, a literature review was conducted and found that DSM criteria (for depression) tend to under diagnose the incidence of depression in PD (Cummings, 1992). Seeing as DSM criteria for depression are frequently used in clinical practice, it is not difficult to imagine why so many PD patients are left untreated with their depression. However, the Beck Depression Inventory (BDI) has proven to be a reliable instrument for measuring depression in PD research (Levin, Llabre, & Weiner, 1988). Therefore, the BDI could be adapted into clinical practice as a screening device so that physicians can more accurately detect depression in their patient.

When a diagnosis of depression is accurately made in PD, many patients are still left untreated because it is not clear, at present, which treatment options (e.g., psychotherapy, antidepressant pharmacotherapy, or electroconvulsive therapy) are safe and effective for this clinical population. As a result, the literature on these separate

therapies will be reviewed in order to gain more insight on why physicians may be reluctant to prescribe an active treatment regimen for their depressed PD patient.

Treatments for Depression in PD

Psychotherapy. There is a consensus among physicians and researchers that psychotherapy can be a helpful treatment modality for PD patients, in general, and especially for those individuals who are suffering from mild and moderate depression (Dakof & Mendelsohn, 1986; Kremmer & Starkstein, 2000; Poewe & Luginger, 1999; Slaughter et al., 2001). For instance, it has been suggested that behavioral therapy around the time of diagnosis of PD and during advanced stages of the illness can adequately control for mood disorders in many PD patients (Poewe & Luginger, 1999). Brown and Jahanshashi (1995) suggested that a psychotherapy program should be adapted to each PD patient in order to prevent and treat the depression that is associated with PD. These researchers further suggested that the psychotherapy program should focus on disability and handicaps produced by PD and be continuous throughout the course of their illness (Brown & Jahanshashi, 1995).

While the importance of psychotherapy appears to be well recognized by the medical community, a literature search of the Medline and Psych-Info abstract indices has generated only two formal studies on the effects of a behavioral-cognitive intervention of any kind for PD patients (Ellgring et al., 1993; Trend, Kaye, Gage, Owen, & Wade, 2002). Ellgring et al. (1993) were the first to systematically explore whether or not PD patients could respond favorably to a psychological intervention. Overall, the researchers observed that psychological counseling aimed at facilitating cognitive restructuring was able to reduce overall stress, improve social functioning, and increase

acceptance of PD. Regrettably, it is not clear whether this intervention would have improved depression in this sample of PD patients because it was not assessed as a health outcome by the researchers (Ellgrig et al., 1993).

Trend et al. (2002) observed that depression scores were significantly reduced for PD patients after receiving relaxation training and individual talks from a multidisciplinary team of therapists (i.e., PD specialist nurse, physiotherapist, occupational therapist, speech therapist, and care manager) over a course of six weeks. Although the researchers observed improvements on mood at post-testing (Trend et al., 2002), it should be noted that none of their patients could be classified as depressed because of their low baseline scores on a non-validated measure of depression (i.e., Hospital Anxiety and Depression Scale) in PD. Therefore, the efficacy of behavioral-cognitive therapy has yet to be established for depressed PD patients. For this reason, it is unlikely that psychotherapy would transcend as a monotherapy for depression in PD.

Antidepressant Pharmacotherapy. The results from several placebo-controlled trials have indicated that antidepressants can alleviate depression in PD (Anderson, Aabro, Gulmann, Hjelmsted, & Pedersen, 1980; Goetz, Tanner, & Klawans, 1984; Laitinen, 1969; Strang, 1965; Wermuth et al., 1998). However, other studies have found antidepressants to be ineffective in PD (Allain, Cougnard, Neukirch, & FSMT members, 1991; Fischer & Baas, 1987; Indaco & Carrieri, 1988; Leentjens, Vreeling, Luijckx, & Verhey, 2003; Przuntek & Kuhn, 1987). Furthermore, the literature also indicates that there is a tangible risk for developing deleterious side effects (e.g., delirium, memory impairment, hypotension, greater motor disability, and seizures) when taking antidepressants in conjunction with standard treatments for the motor aspects of PD

(Drevets, 1994; Preskorn, 1993; Zesiewics, Gold, Chari, & Hauser, 1999). As a result, physicians may be reluctant to prescribe antidepressants to PD patients unless they present with severe affective disturbances (Edwards et al., 2002). As can be imagined, this leaves the patient in an uncomfortable position to cope with the negative emotional affect that they are experiencing concurrent to the physical disability produced by PD.

Electroconvulsive therapy. The potential benefits of electroconvulsive therapy (ECT) have also been explored as a treatment modality for PD patients suffering from depression. A literature review of studies conducted between 1975 and 1991 has provided evidence that depression can be reduced in most PD patients who are treated with ECT (Faber & Trimble, 1991). More specifically, it was observed that approximately 70% of PD patients showed improvements in psychiatric disturbances (including depression) across the 21 studies that were reviewed (Faber & Trimble, 1991). In a more recent study conducted on 25 PD patients, it was similarly observed that depression was significantly reduced following ECT treatment (Moellentine et al., 1998).

One reason why ECT can serve as a viable treatment option for depressed PD patients is that electrically induced seizures can increase both norepinephrine and serotonin levels in the brain (Poewe & Seppi, 2001). Because it has been observed that norepinephrine increases dopamine levels in the basal ganglia and reduces PD motor symptoms, many psychiatrists/physicians would have the potential to improve affective and motor function in their PD patients with this treatment. In support of this notion, several studies have found an improvement on motor symptoms after ECT has been applied to PD patients (Douyone, Serby, Klutchko, & Rotrosen, 1989; Friedman & Gordon, 1992; Mollentine et al., 1998).

While these positive outcomes seem to suggest that ECT can serve as a preferential treatment to antidepressant therapy, there is also evidence to suggest that there is a tangible risk for developing deleterious side effects such as delirium (Moellentine et al., 1998) and even death with ECT use in PD (Friedman & Gordon, 1992). Accordingly, many physicians may not consider using ECT as a first line therapy unless their PD patients were self-destructive and non-responsive to drug therapy (Kim & Hershey, 1988). Because the majority of depressed PD patients tend to suffer from mild to moderate depression and are not suicidal (Slaughter et al., 2001), ECT would not translate into a viable treatment option for most of this clinical population. Consequently, these mild to moderately depressed PD patients may be left untreated to cope with the negative emotional affect that they are experiencing unless a safe and effective approach to treatment emerges from the PD literature.

Prospective Goals for this Review

The purpose of this review is to examine the most viable treatment option for depression in PD. This will be done so that a meta-analysis of this literature can be conducted and possibly allow more patients to be actively treated within the clinical care setting. Unfortunately, there is an insufficient amount of evidence to make a conclusion about the efficacy of psychotherapy in the treatment of depression in PD. Furthermore, depression in PD has been related to neurological disease (Cummings, 1992). Therefore, it is unlikely that psychotherapy would be used as a first line intervention for the treatment of depression in PD. Although antidepressants have produced mixed results in PD, there are many studies to draw valid conclusions about their therapeutic effect (see Table 1). Moreover, because depression has been attributed to deficits in noradrenergic

(Hornkiewicz, 1982) and serotonergic systems (Hornykiewicz 1982; Mayeux et al., 1984), it is not hard to imagine why antidepressants are the most studied treatment option within the PD literature. This extensive focus might suggest that antidepressants would serve as the most viable treatment option within the clinical care setting. As a result, the focus of this review will be on the current issues pertaining to antidepressant use in PD.

I will also discuss the negative health consequences that have been associated with depression in PD. This will be done in order to provide a reasonable basis for meta-analyzing health outcomes outside of depression so that antidepressant therapy may serve as a method for improving the overall health status of PD patients. Additionally, I will discuss the safety and efficacy of antidepressants in PD, and formally discuss why a meta-analysis should be conducted on this literature. All things considered, it is hoped that what will be learned from this research can be quickly adapted into clinical practice because many PD patients are in need of both a safe and effective treatment for their physical and psychological health.

Depression and Associated Health Outcomes in PD

Depression and Pain. Pain is considered to be a common problem which often overshadows the motor symptoms of PD. Its prevalence has been estimated to range between 40 and 68% in levodopa-treated patients (Ford, 1998; Goetz, Tanner, Levy, Wilson, & Garron, 1986; Waseem & Gwinn-Hardy, 2001). Although the symptoms of pain are quite variable in PD, it has been reported that the most burdensome aspects are musculoskeletal cramps, dystonia, and joint pains (Goetz et al., 1986). While the high prevalence of pain in PD has generally been attributed to motor fluctuations due to the on-off periods that occur with levdopa treatment (Waseem & Gwinn-Hardy, 2001) and to

the increased motor disability (e.g., limb rigidity) that is associated with advancing disease (Goetz et al., 1986), there is also evidence to support the notion that depression may exacerbate pain in PD.

Karlsen, Larsen, Tandberg, and Macland (1999) observed that the best predictor of pain in PD as assessed through the Nottingham Health Profile (NHP) was depressive symptoms ($p < .01$) and more advanced disease ($p < .01$). However, it should be noted that depression and more advanced disease only explained 17% of the variance found in the NHP pain scores (Karlsen et al., 1999). In a similar study, it was observed that pain scores as assessed through the specific Parkinson's disease questionnaire (PDQ-39) were significantly higher ($p < .01$) for depressed than non-depressed PD patients (Schrag, Jahanshahi, & Quinn, 2001). Similarly, pain scores as assessed through the Parkinson's disease quality of life questionnaire (PDQL-37) was also significantly associated with the worsening of depressive symptoms (Hobson, Holden, & Meara, 1999). Taken together, it appears that there is a relationship between depression and increased pain in PD. Therefore, the correct management of pain in PD may reside in the resolution of depression. Regrettably, there are few studies assessing the benefits of antidepressants for pain in PD. As a result, it is not clear whether or not a treatment designed to reduce depression in PD will similarly increase pain thresholds for this clinical population. Nonetheless, there is evidence to suggest that antidepressants may be helpful since an association between serotonin, pain, and depression has been found in PD (Urakami et al., 1990).

Urakami et al. (1990) observed that PD patients complaining more frequently about pain and depression had significantly reduced levels of serotonin in their

cerebrospinal fluid (CSF) relative to those PD patients that did not complain about pain. Therefore, it can be inferred from this study that by increasing serotonin levels in the central nervous system with antidepressants, both depression and pain may be reduced for many PD patients.

Depression and Anxiety. The incidence of anxiety is also high in PD, with a prevalence rate of 38% (Lamberg, 2001). The most frequent symptoms of anxiety in PD are constant feelings of fear, incessant uncontrollable worrying, and a host of physical symptoms such as muscle tension, palpitations, sweating, and shortness of breadth (Hurwitz & Calne, 2001). Interestingly, the research shows that both anxiety and depression are closely associated in PD (Henderson, Kurlan, Kersun, & Como, 1992; Menza, Robertson-Hoffman, & Bonapace, 1993).

Henderson et al. (1992) administered a self-report survey to 164 PD patients and 150 age-matched healthy control subjects. Overall, the researchers found that the prevalence of depression concurrent with symptoms of panic/anxiety was significantly higher in PD patients relative to the control subjects (38% vs. 8%). Furthermore, it was found that depression and anxiety were significantly associated, whereas the clinical features of PD (e.g., disease severity and duration) were not related to anxiety. This suggests that both depression and anxiety may be related to the neurochemical disturbances that are produced by PD and that antidepressants may be effective at treating both psychiatric disorders.

Menza et al. (1993) also examined the frequency of anxiety and depressive symptoms in 42 patients with PD, and observed that 29% of this sample suffered from an anxiety disorder. Moreover, of the 29% who suffered with anxiety, 92% had a comorbid

depressive disorder. The researchers also conducted a stepwise regression analysis and found that depression significantly accounted for 44% of the variance in anxiety scores. Interestingly, however, the severity of PD or levodopa dosage did not significantly predict levels of anxiety in PD patients. The researchers concluded that the symptoms of depression and anxiety may be a function of neurochemical changes as opposed to a psychological reaction to illness or side effects due to levodopa usage. Taken together, it appears that depression is a risk factor for the development of anxiety in PD patients. Therefore, it is possible that both psychological outcomes share the same neurochemical substrate—namely, serotonin.

There have been two studies directly linking serotonin to depression and anxiety in PD (Menza, Palermo, DiPaola, Sage, & Ricketts, 1999; Menza, Marin, Kaufman, Mark, & Lauritano, 2004). Menza et al. (1999) examined depression and anxiety scores in PD patients as a function of the variation in a specific serotonin transporter gene (short allele), which normally prevents the synthesis of serotonin and is a source of the anxiety and depression. The researchers found that PD patients with the short allele of the serotonin gene were more likely to have higher anxiety and depression scores than those PD patients without the gene. On this note, because serotonin is involved with both psychological outcomes, it is plausible that a treatment which increases serotonin (i.e., antidepressants) can alleviate depression and anxiety in PD.

Menza et al. (2004) tested the above notion that a treatment specifically aimed at influencing serotonin will influence both depression and anxiety in PD patients. The researchers conducted an 8-week open-label trial using the SSRI citalopram on 10 depressed PD patients. Overall, the researchers found that depression scores improved

significantly and was associated with significant improvements in anxiety symptoms. The researchers concluded that treating depression in patients with PD will also lead to improvements on anxiety.

Depression and Cognition. Cognitive deficits are common in non-demented patients with PD (for reviews, see Morrison et al., 2000; Raskin et al., 1990). However, the literature also shows that depression can further exacerbate these cognitive deficits (Dalrymple-Alford, Kalders, Jones, & Watson, 1994; Lombardi, Woolston, Roberts, & Gross, 2001). For instance, it was observed that PD patients with mild depression had significantly greater impairments on attention and working memory relative to non-depressed PD patients (Uekermann et al., 2003). Interestingly, the researchers also observed that the depressed PD group was not significantly different on cognitive functioning relative to a non-neurologically ill depressed group (Uekermann et al., 2003). As a result, the researchers concluded that some of the cognitive impairments found in PD could represent the effects of depression alone rather than a combination of neurological disease and depression (Uekermann et al., 2003). This notion is further supported by neurological evidence, which shows similar regional abnormalities between depressed PD and non-neurologically ill depressed patients (Kuzis et al., 1997; Starkstein et al., 1989; Troster et al., 1995; Wertman et al., 1993).

The results from several neuroimaging studies have consistently shown that depressed PD patients and non-neurologically ill depressed patients evidence greater metabolic abnormalities in frontal and temporal lobes relative to non-depressed PD patients (Kuzis et al., 1997; Starkstein et al., 1989; Troster et al., 1995; Wertman et al., 1993). However, other researchers have argued against this unilateral hypothesis because

similarities between depressed PD patients and non-neurologically ill depressed patients have not been found in studies using neuropsychological testing. For instance, Norman, Troster, Fields, and Brooks (2002) examined the influence of depression on the cognitive/behavioral functioning of PD patients using the Mattis Dementia Rating Scale (DRS). Overall, the researchers observed that there were no differences observed on certain frontal/executive functions (i.e., initiation, preservation, and conceptualization) between the PD groups (depressed and non-depressed) and the non-neurologically ill depressed group. It was concluded by these researchers that depression alone or PD itself might play independent roles in certain types of executive dysfunction (Norman et al., 2002). Alternatively, they suggested that depression might further exacerbate the cognitive impairments already found in PD (Norman et al., 2002).

Another explanation for the increased prevalence of frontal/executive dysfunction in depressed PD patients might be attributed to frontostriatal circuit dysfunction. More specifically, the orbitofrontal cortex (OFC) is a specific subsystem of the frontostriatal circuit that has been associated with depression (Cummings, 1993; Tekin & Cummings, 2002) and the dorsolateral prefrontal cortex (DLPFC) is another subsystem that has been related to frontal/executive cognitive function (Zgaljardic, Borod, Foldi, & Mattis, 2003). On this note, it has been observed that depressed PD patients perform more poorly on neuropsychological tests that tap into frontal/executive function (i.e., Wisconsin Card Sorting Test and Raven Progressive Matrices) relative to nondepressed PD patients (Kuzis et al., 1997). Moreover, it has been reported that depression in PD is associated with decreased activation of the OFC (Cummings, 1993; Zgaljardic et al., 2003), and that lesions to the DLPFC will produce deficits in sustained attention, working memory,

and/or set maintenance and shifting in response to changing task demands (Zgaljardic et al., 2003). Thus, the link between depression and increased frontal/executive dysfunction in depressed PD patients may be attributed to greater neurological impairment than what is typically found in the frontostriatal circuit of nondepressed PD patients.

In addition to frontal/executive dysfunction, there is also evidence to suggest that depression may be related to general memory loss. In particular, it has been reported that many depressed PD patients tend to develop dementia (Playfer, 1999). For instance, in a large-scale community based survey of dementia in PD, it was estimated that dementia occurred in 27% of patients (Aarsland, Tandberg, Larsen, & Cummings, 1996). The researchers also observed that major depression was significantly greater in the demented patients (23%) relative to the PD patients without dementia (2.3%). Other studies have bolstered these findings in that depression at baseline increases the risk for later developing dementia in PD (Hughes et al., 2000; Stern, Marder, Tang, & Mayeux, 1993). Additionally, it has been observed that treating PD-related depression can improve memory (Mayeux et al., 1981; Starkstein & Robinson, 1991).

All in all, it can be concluded that more research needs to be conducted in order to delineate the relative importance of depression and PD on the frontal/executive and memory processes in this clinical population. Nonetheless, whether depression accounts for half or even all of the variance, it is clear that depression and cognitive impairments are associated in PD. Therefore, by treating PD with antidepressants, it is plausible that cognitive (e.g., attention and memory) and affective functioning may improve for many patients.

Depression and Sleep. Sleep-related problems are a common complaint in PD with a prevalence ranging from 67-98% (Askenasy, 1993; Chokroverty, 1996; Kryger, Roth, & Dement, 1994; Lees, Blackburn, & Campbell, 1988; Tandberg, Larsen, & Karlsen, 1998). Specifically, the literature shows that both sleep initiation and maintenance are serious problems reported by many PD patients (Apps, Sheaff, Ingram, Kennard, & Empey, 1985). Furthermore, when sleep is interrupted, many PD patients tend to lie awake for a significant amount of time (Apps et al., 1985; Factor, McAlarney, Sanchez-Ramoz, & Weiner, 1990). Together, these findings suggest that the overall quality of sleep in PD is poor enough to be considered a serious disorder, and several explanations have been put forward to help understand why PD patients have a hard time initiating and maintaining sleep.

While neurodegenerative processes (i.e., reduced neurophysiological activity in the systems involved with sleep regulation), difficulties in breathing (i.e., sleep apnea), motor restriction (e.g., difficulties turning in bed), medication side effects (e.g., increased nightmares), and pain (e.g., leg cramps) have all been proposed as risk factors for the occurrence of sleep problems in PD (Happe, Ludemann, & Berger, 2002), depression is also related to sleep disorder in this clinical population . For instance, a survey conducted on 100 PD patients revealed that depression was significantly associated with sleep disturbances (Partinen, 1997). Starkstein, Preziosi, and Robinson (1991) similarly found that depressed PD patients had significantly more sleep disturbances than non-depressed PD patients. Furthermore, these researchers observed that depression scores accounted for most of the variance in the sleep disorders of PD patients relative to any other clinical variable (Starkstein et al., 1991). In a similar study conducted on 116 PD patients (Happe

et al., 2002), it was observed that depression was significantly associated with sleep onset difficulties (p=.02) and sleep interruptions (p=.01). These researchers concluded that depression is a serious risk factor for sleep- related problems, and that antidepressants may be a helpful treatment modality (Happe et al., 2002).

It is clear that depression is related to sleep disorder in PD. While hypnotic agents, such as benzodiazepines or barbiturates, are generally efficacious in treating sleep disturbances in patients without neurological disease, their use in PD is generally avoided because of the associated risks. More specifically, hypnotic agents can produce memory impairments, difficulty with attention, sleep apnea, daytime drowsiness, dizziness, fatigue, and addiction (Maxmen & Ward, 1995). Moreover, hypnotic agents can negatively interact with antidepressants and medications used for treating PD (Maxmen & Ward, 1995). Accordingly, it is important to examine whether or not antidepressant treatment alone can alleviate both depression and sleep disorder in PD so that their overall quality of life may improve.

Depression and Health-Related Quality of Life. The term health-related quality of life has been used to describe the distress and functional impairment that is produced by a chronic debilitating illness. Currently, there are several scales that have been used to measure health related quality of life in PD, both generic and disease specific (Bergner, Bobbitt, Carter, & Gilson, 1981; Jenkinson, Fitzpatrick, & Argyle, 1988; Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995). Overall, the research using these generic and disease specific scales has found motor disability to be an important determinant of reduced health-related quality of life in PD (Dodel, Berger, & Oertel, 2001; Keranen et al., 2003; Peto et al., 1995). However, there is also a growing body of literature which shows that

even beyond motor disability, depression can be a risk factor for reduced quality of life in PD.

Karlsen et al. (1999) used the Nottingham Health Profile (NHP) to determine which clinical features reduce the overall health-related quality of life in PD. Briefly, the NHP is a generic, health related quality of life questionnaire that consists of six dimensions--namely, emotional reactions, energy, pain, physical mobility, sleep, and social isolation (Jenkinson et al., 1995). Overall, these researchers observed that depression was related to negative emotional reactions, low energy, pain, and social isolation (Karlsen et al., 1999). Interestingly, depression was not related to physical mobility problems and sleep disorders on the NHP. This finding is contradictory to the above evidence which shows that depression is a tangible risk factor for both motor disability and sleep disorders in PD. Nonetheless, other studies using PD-specific measures of health-related quality of life have found a relationship between depression and these health outcomes (Hobson et al., 1999; Schrag et al., 2001).

Schrag et al. (2001) used the 39-item Parkinson's Disease Questionnaire (PDQ-39) to determine whether or not depression is related to poorer health-related quality of life in this clinical population). Briefly, the PDQ-39 is a PD- specific, health-related quality of life questionnaire that consists of eight dimensions of health -- namely, mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort (Peto et al., 1995). Overall, the researchers found that depressed PD patients scored significantly more poorly on all eight dimensions of the PDQ-39 relative to non-depressed PD patients. Furthermore, it was observed that after controlling for PD disability, depression significantly correlated with

all areas of health-related quality of life on the PDQ-39. This relationship between depression and reduced health-related quality of life on the PDQ-39 is also supported by an earlier study that was conducted by Shrag, Jahanshahi, and Quinn (2000). The researchers found that depression was significantly correlated with reduced health-related quality of life on the PDQ-39.

Additional evidence deriving from another disease specific scale has offered greater reliability to the notion that depression is a serious risk factor for reduced health-related quality of life found in PD. Hobson et al. (1999) developed the Parkinson's Disease Quality of Life Questionnaire (PDQL) to determine which clinical and demographic variables are related to health-related quality of life in PD. Briefly, the PDQL is a PD-specific, health-related quality of life questionnaire that consists of four dimensions of health -- namely, parkinsonism symptoms, systemic symptoms, social functioning, and emotional functioning). Once again, it was observed that depression was the best predictor of poorer health-related quality of life along all four dimensions of the PDQL relative to age, disease severity, and cognitive impairment.

Depression is a risk factor for overall health-related quality of life in PD, and especially for the health domains of motor impairment, pain, sleep, anxiety, and cognition. Therefore, it is expected that overall health-related quality of life would improve once depression in PD is alleviated. While antidepressant treatment can be used as a therapy, one problem with its use in PD is that patients tend to be elderly and are often administered a range of medications that can lead to deleterious side effects (Cummings & Masterman, 1999). For this reason, a meta-analysis should be conducted so that the safety and efficacy of antidepressants can be established on the health

outcomes of all PD patients. Accordingly, the next section of this paper will examine the health outcomes that are associated with antidepressant use in PD. Moreover, there will be a discussion of why a research synthesis should be conducted on this literature.

Antidepressants and Health Outcomes in PD

Tricyclic Antidepressants. A review of the aforementioned studies has revealed that depression in PD can further complicate our understanding of the pathophysiology of motor impairment in this disease. Specifically, if our assumption of the cause for motor impairment in PD is correct, that is, reduced dopamine impairs motor functioning (Cummings, 1992), then why would depression, which has been primarily related to serotonin functioning (Mayeux, Stern, Cote, & Williams, 1984; Edwards et al., 2002), correlate with the motor aspects of this disorder? For instance, it has been observed that individuals who were not depressed initially but became depressed within a year showed a significantly greater increase in motor disability compared to those PD patients who were never depressed throughout the course of their illness (Brown, MacCarthy, Gotham, Der, & Marsden, 1988). Starkstein et al. (1990) similarly found that after a 1-year follow-up evaluation period, 67% of the major depressed patients had progressed to the next stage of PD (i.e., Hoehn & Yahr staging) as compared to 41% of the patients with minor depression and 20% of the non-depressed patients. Thus, it appears that there is a dose-response relationship between the severity of depressive symptoms and physical disability in PD. Interestingly, some studies have even shown that motor disability can improve once depression is treated with tricyclic antidepressants (TCAs).

Strang (1965) conducted a double-blind study on the effects of imipramine (150-250 mg/day) in PD and found that depression improved for 60% of PD patients.

Moreover, it was found from this study that antidepressant therapy had a beneficial effect on rigidity, tremors, and akinesia. Other studies have bolstered these findings in that motor deficits were reduced once depression was treated with antidepressants. An early double-blind study was conducted on the effects of desipramine (100mg/day) in PD, and reductions in rigidity and tremors occurred for those patients whose depression responded favorably to antidepressant treatment (Laitnen, 1969). Together, these results suggest that depression and motor impairment may be associated in PD, and that TCAs may be efficacious in treating both depression and motor disability for this neuropsychiatric population.

One explanation for the association between improved depression and motor impairment from the above studies (Strang, 1965; Laitnen, 1969) is that imipramine and desipramine (as well as nortiptyline [Anderson et al, 1980] and amitriptyline [Indaco & Carrieri, 1988]) block the reuptake of norepinephrine (Maxim & Ward, 1995). This mechanism of action with these TCAs on norepinephrine (NE) is important because recent evidence has related NE to parkinsonian symptoms and dopamine levels within the basal ganglia. More specifically, it has been observed that there is a progressive loss of noradrenergic neurons in the locus coeruleus of PD patients (Gesi et al., 2000). Moreover, in animal models of PD, it has been shown that drugs which increase the concentration of NE in the locus ceoruleus (i.e., 2-methoxy idazoxan) also reduce parkinsonian symptoms (i.e., catalepsy), and increase dopamine levels in the basal ganglia of rats (Srinivassan & Schmidt, 2004; Srinivasan & Schmidt, 2003). Therefore, by blocking the reuptake of NE, the TCAs that will be examined in this meta-analysis (see Table 1) may improve motor function in PD patients by facilitating the release of

dopamine in the basal ganglia. We predict that a meta-analysis would reveal a positive and significant effect size result for depression and motor function for PD patients receiving TCAs.

While TCAs have proven useful in treating depression and partially restoring physical functioning (Anderson et al., 1980; Laitinen, 1969; Strang, 1965), many patients cannot tolerate them. Adverse events with TCAs in PD and other patients are cardiac arrhythmias, orthostatic hypotension, sedation and memory impairments (Poewe & Seppi, 2001). At high doses, TCAs can produce confusional states, hallucinosis, and delirium (Poewe & Seppi, 2001) in depressed PD patients. Therefore, the safety of TCAs has to be judged carefully in PD patients by examining the magnitude and significance of TCAs on all of the above health outcomes.

Serrotonin Re-Uptake Inhibitors. There have been several clinical trials examining the effects of serotonin re-uptake inhibitors (SSRIs) in PD. Hauser and Zesiewicz (1997) conducted a 7-week open-label trial that examined the effects of sertraline (25-50mg/d) in 15 PD patients who were suffering with either minor or major depression. Overall, the researchers found that there was a significant decrease in depression scores between the baseline and posttest periods. However, unlike the TCA studies described earlier, sertraline did not improve motor performance as measured by the Unified Parkinson's Disease Rating Scale (UPDRS). The researchers also observed that sertraline produced several minor adverse reactions in PD patients -namely, insomnia, light headedness, and sexual dysfunction. There have also been two recent open-labeled clinical trials which have examined the effects of paroxetine for depression in PD (Ceravolo et al., 2000; Tesei et al., 2000). Once again, these studies found that

SSRIs were able to reduce depression, but there was also evidence of a deterioration of motor symptoms in many of the PD patients (Ceravolo et al., 2000; Tesei et al., 2000). Moreover, paroxetine seemed to produce several minor adverse reactions which included nausea, anxiety, agitation, confusion, dizziness, palpitation, paraesthesia, and headache (Ceravolo et al., 2000; Tesei et al., 2000).

Taken together, it appears that SSRIs can be effective at treating depression in PD. However, the salutary benefits that were seen with TCAs on motor disability (Anderson et al., 1980; Goetz et al., 1984; Klaasen et al., 1995; Laitinen, 1969; Strang, 1965) are contradictory to what SSRIs have produced--namely, an increase in motor symptoms. Thus, the question remains as to whether or not SSRIs can exacerbate parkinsonian symptoms.

Overall, the research has produced mixed results, with some studies showing deteriorations on PD motor symptoms (Ceravolo et al., 2000; Jimenez et al., 1994; Steur, 1993), and others not observing ill effects after the use of SSRIs (Caley & Friedman, 1992; Hauser & Zesiewicz, 1997; Montastruc et al., 1995). However, one problem with all of the SSRI literature cited from above is that they used low constraint research methods, that is, case reports and open labeled trials. Therefore, it cannot be concluded with certainty that SSRIs are effective in treating depression or that they are exacerbating the motor symptoms of PD. Fortunately, there are three published placebo-controlled trials which have assessed the effects of SSRIs on the depressive and motor symptoms of PD patients (Leenjens, Vreeling, Luijckx, & Verhey, 2003; Rampello, Chiechio, Raffaele, Vecchio, & Nicoletti, 2002; Wermuth et al., 1998).

Wermuth et al. (1998) conducted a placebo-controlled trial on PD patients suffering with major depression. The researchers administered the SSRI citalopram or a placebo to an average of 10 subjects in each group over the course of 52 weeks. It was observed that there were no significant group differences in measures of depression (i.e., Hamilton Depression Scale [HDS]), motor function (i.e., UPDRS), and adverse side effects (i.e., UKU Side Effects Scale). Leentjens et al. (2003) also conducted a study using the SSRI citalopram (n=6) or placebo (n=4) on severely depressed PD patients. Once again, it was observed that there were no significant group differences in measures of depression (i.e., Montgomery-Asberg Depression Rating Scale [MADRS]) or motor function (i.e., UPDRS).

It was observed from another study that citalopram was able to improve motor performance (i.e., bradykinesia and finger tapping speed) for both depressed (n=18) and non-depressed (n=14) PD patients relative to a non-depressed placebo (n=14) control group (Rampello et al., 2002). The researchers also observed that depression was significantly reduced for the entire depressed PD subgroup (Rampello et al., 2002). However, this reduction in depression may be attributed to a placebo effect given that the research described earlier observed similar findings with low constraint methods (Ceravolo et al., 2000; Hauser & Zesiewicz,1997; Tesei et al., 2000).

Taken together, it may be concluded from these randomized controlled trials that SSRIs may not be effective at alleviating both the depression and motor symptoms of PD (Leenjens et al., 2003; Wermuth et al., 1998). On the other hand, it also possible to attribute these null results to a lack of proper statistical power because of the small samples used within each of the two placebo controlled trials (Leenjens et al., 2003;

Wermuth et al., 1998). On this note, it has been argued elsewhere that the null hypothesis could never be supported given that an effect size is seldom equal to zero (Cohen, 1994). Therefore, it is clear that a meta-analysis can provide the opportunity for positive effects to emerge and contribute to the overall picture of a research enterprise (i.e., the safety and efficacy of antidepressants in PD)beyond what is produced by the null hypothesis statistical testing procedure (NHST).

Monoamine-Oxidase Inhibitors. The biomedical approach has attributed PD related depression to a deficit in dopaminergic (Mayeux, 1992), noradrenergic (Hornykiewicz, 1982), and serotonergic brainstem ascending systems (Hornykiewicz, 1982; Mayeux et al., 1984). As a result, inhibition of monoamine oxydase (MAO) does not seem like an unreasonable approach to the treatment of depression in PD. However, it should be noted that MAO can exist in two forms—namely, MAO-A and MAO-B inhibition. The MAO-A isoform is selective for noradrenaline and serotonin metabolism, whereas MAO-B inhibition is selective for dopamine. A literature search of the Medline and Psych-Info abstract indices has identified studies on both the inhibition of MAO-A through moclobemide and MAO-B through selegiline.

Moclobemide is a reversible competitive inhibitor of the enzyme MAO-A, which, in turn, increases noradrenaline and serotonin brain concentrations. It is this increase that is responsible for moclobemide's antidepressant effect (DaPrada, Kettler, Burkard, Muggli-Maniglio, & Haefely, 1989). At present, there are no placebo-controlled trials assessing this drug as an antidepressant in PD. The only randomized control trial identified by this review was a study that compared moclobemide and selegiline in PD. Steur and Ballering (1997) randomly assigned 10 PD patients suffering with major

depression to a moclebemide (600 mg a day) monotherapy group or moclobemide (600 mg a day) plus selegiline (10 mg a day) group. Overall, it was found that improvement in the combined moclobemide-selegiline group was significantly more pronounced than in PD patients receiving only moclobemide. Furthermore, many PD patients in the combined treatment group evidenced improvements on motor symptoms and cognitive function as measured by the Mini Mental State Examination (MMSE). Unfortunately, it was not reported if improvements on depression scores occurred from baseline to the posttest period in the moclobemide monotherapy group. Thus, no inferences can be made about the efficacy of moclobemide as an antidepressant in PD. However, given that the combined treatment group evidenced significant improvements on depression, cognition, and motor function, it is likely that selegiline provided most of the salutary health benefits found in this sample of depressed PD patients.

When selegiline is given at its usual clinical dose of 10 mg a day or less in PD, it can serve as an irreversible inhibitor of brain MAO-B enzyme. Accordingly, it is expected that selegiline at 10 mg a day will increase dopamine levels, which in turn can delay the need of symptomatic therapy in early PD or improve motor function in advanced patients (Parkinson Study Group; 1993). Thus, selegiline at its usual clinical dose may not exert an antidepressant effect because it is selectively inhibiting MAO-B (and not MAO-A) enzymes in the adult human brain. Nonetheless, it should be noted that selegiline was initially introduced as an antidepressant because the drug can also act as a MAO-A inhibitor when given at slightly higher doses (Sunderland et al., 1985).

Quitkin et al. (1984) tested the effects of selegiline (20 mg a day) on 17 atypical depressives without PD and found that improvement occurred for 60% of patients. Mann

et al. (1989) conducted a double-blind placebo-controlled trial testing the effects of selegiline on patients suffering with primary depression. Overall, the researchers found that depression was significantly reduced for depressed patients assigned to the selegiline relative to the placebo control group. They also found that a significantly greater reduction of depression scores occurred with higher ($\geq$ 30 mg) than with lower ($\leq$ 30 mg) doses of selegiline. Taken together, it appears that selegiline can serve as an efficacious antidepressant at higher doses in depressed patients without neurological disease. However, its use at higher doses in PD is sparse, and the focus of selegiline research has been restricted to MAO-B inhibition.

While MAO-B inhibition is selective for dopamine metabolism and would be expected to improve motor function, there are several studies testing selegiline's antidepressant effects at lower doses. For instance, Allain et al. (1991) conducted a double-blind, placebo-controlled trial testing the effects of selegiline (10 mg a day) on 93 PD patients suffering with depressive symptoms. Overall, the researchers found that the selegiline group showed significant improvements on motor functioning and depression relative to the placebo group at the end of 3 months. Additionally, it has been observed from another sample of PD patients that selegiline (10 mg per day) significantly reduced depression and improved motor performance relative to PD patients assigned to a placebo control group (Allain, Pollak, & Neukirch, 1993).

Taken together, it is not clear why selegiline would improve depression at a dose of 10 mg a day in PD patients (Allain et al., 1991; Allain et al., 1993), particularly when other studies have shown that the drug is ineffective at treating depression at doses lower than 20 mg a day in non-neurologically ill patients (Quitkin et al.,1984; Mann et al.,

1989). One explanation for these discrepant results is that the PD patients affective function improved only because their motor dysfunction was reduced with selegiline (Allain et al., 1991; Allain et al., 1993). In support of this notion, Dalrymple-Alford et al. (1995) conducted a double-blind placebo controlled trial using selegiline at a similar dose on depressed PD patients and found no significant changes on motor scores or depression relative to the placebo control group. However, it should be noted that the Dalrymple-Alford et al. (1995) study only tested 20 PD patients overall as opposed to the 90 plus subjects used in above studies (Allain et al., 1991; Allain et al., 1993). Therefore, the null results from the Dalrymple-Alford et al. (1995) study may be attributed to a lack of proper statistical power and a meta-analysis may possibly reveal a positive effect on both health outcomes.

At present, it is not clear whether selegiline can have a real antidepressant effect at a dose where it is selectively inhibiting the MAO-B enzyme in PD patients. Interestingly, there is some literature implicating dopamine with depression. For instance, it has been observed that other selective MAO-B inhibitors (Parkinson Study Group, 1994) and D2/D3 agonists (Corrigan, Denahan, Wright, Ragual, & Evans, 2000; Reichmann, Brecht, Koster, Kraus, & Lemke, 2003; Rektorova et al., 2003) have reduced depression in non-neurologically ill patients and in PD patients. Accordingly, because dopamine agonists can reduce depression (Corrigan et al.,2000; Reichmann et al., 2003; Rektorova et al., 2003), then it may be logical to assume that selegiline may have the potential to serve as both an antidepressant and antiparkinsonian agent through its effects on MAO-B inhibition.

Altogether, there are numerous studies examining selegiline's effects on depression and/or motor function. A meta-analysis of this literature would help to determine selegiline's therapeutic effect in PD. Accordingly, if selegiline does not produce a positive and significant effect size result for depression, but does so for motor functioning, then it can be concluded that selegiline does not have any real antidepressant effects at 10 mg daily in PD patients. Alternatively, if selegiline improves both health outcomes as evidenced by positive and significant effect size results, this finding would add to the growing body of literature implicating reduced dopamine as a plausible etiological factor in PD-related depression (Mayeux, 1992; Parkinson Study Group, 1994; Rektorova et al., 2003). Therefore, a meta-analysis of this literature can be helpful in establishing both selegiline's antidepressant and antiparkinsonian effects as an MAO-B inhibitor and can further contribute to the understanding of the etiology of depression in PD.

Although selegiline at 10 mg a day has produced mixed results for depression in PD, it is important to note that several studies have consistently shown that this drug can produce many adverse effects such as nausea, dizziness, fatigue, constipation, insomnia, and hypotension (Churchyard, Mathias, Bookonchuen, & Lees, 1997; Heinonen & Myllyla, 1998). While these adverse events are relatively mild, they can reduce the quality of life for many PD patients. Furthermore, there is controversy on whether or not there is an increase in the risk of death associated with taking selegiline at a dose of only 10 mg a day when taken in conjunction with levodopa (Olanow et al., 1998; Thorogood, Armstrong, Nichols, & Hollowell, 1998). This observation might explain why there has been only one published study testing this MAOI at a dose of 30 mg a day (Hietanen,

1991). However, it should be added that this sample of PD patients was not taking levodopa and was early in the course of the disease (Hietanen, 1991).

Ives et al. (2004) recently conducted a meta-analysis to assess the safety and efficacy of all MAO-B inhibitors in non-depressed patients with early PD. While this meta-analysis revealed that MAOI-B inhibitors produced salutary health benefits, one problem is that it only included published studies with a focus solely on early PD. More specifically, the results from 17 randomized clinical trials revealed that MAOIs (including selegiline) did not significantly increase mortality rates relative to PD patients receiving placebo's (20% vs. 21% deaths; odds ratio = 1.13, p=.20). The meta-analysis also revealed that clinical disability across five clinical trials was significantly improved for the selegline relative to the placebo control group (mean odds ratio = 1.8, $p < .001$). As expected, it was observed that side effects were reported more frequently in PD patients randomized to an MAO-B inhibitor relative to placebo (odds ratio = 1.36, $p < .05$). Therefore, it can be concluded from this research that selegiline and other MAOIs can improve motor function without increasing the risk of mortality in patients suffering with early PD.

In line with the positive results obtained from the initial meta-analysis (Ives et al., 2004), it is hoped that all PD patients can benefit from selegiline. More specifically, mortality, side effects, cognition, affect, and motor functioning will be examined in patients ranging from early to late PD, and in depressed and non-depressed patients. Additionally, this study will be improved from the previous meta-analysis (Ives et al., 2004) by including unpublished literature. This will be done to reduce the upward bias that occurs from using published studies only--namely the file drawer problem. All things

considered, this meta-analysis should be the most comprehensive research synthesis on selegiline's therapeutic effect in PD.

The Purpose of the Current Study

It is clear that there are many discrepancies in the literature on whether antidepressants are safe and effective in treating depression in PD. While TCA's seem to produce the most consistent findings in that depression and motor function are improved, TCAs also produce many adverse events that can further reduce the health-related quality of life for many PD patients (Anderson et al., 1980; Goetz et al., 1984; Klaasen et al., 1995; Laitinen, 1969; Poewe & Seppi, 2001; Strang, 1965). In terms of SSRI's, the literature shows that this class of antidepressants may not be efficacious in treating depression (Leenjens et al., 2003; Rampello et al., 2002; Wermuth et al., 1998). However, one major problem identified with the SSRI literature in this review was that small samples were used, which in turn could increase the likelihood of making Type-II errors. Finally, the research on MAOIs revealed that selegiline may be effective at treating both depression and motor symptoms in PD (Allain et al., 1991; Allain et al., 1993), but serious side effects may be associated with this drug (Ives et al., 2004).

Another common problem that was identified from this review is the issue of proper statistical power. None of the studies within the PD-antidepressant literature have conducted a test for statistical power. This issue may account for some of the discrepancies observed within the SSRI and MAOI literature. A meta-analysis can reveal a positive effect size result even when the null hypothesis is accepted by the NHST procedure. This point has been illustrated by Rosnow and Rosenthal (1989), who

presented an example of how the isolation of studies in the NHST approach (combined with power issues) can wreak havoc in science. Rosnow and Rosenthal (1989) wrote:

> Smith conducts an experiment (with N=80) to show the effects of leadership style on productivity and finds that style A is better than B. Jones is skeptical (because he invented style B) and replicates (with N=20). Jones reports a failure to replicate; his *t* was 1.06, df=18, p>.05. It is true that Jones did not replicate Smith's p value. However, the magnitude of the effect obtained by Jones (*r*=.24 or *d*= .50) was identical to the effect obtained by Smith. Jones had found exactly what Smith had found even though the p values of the two studies were not very close. Because of the smaller sample size of 20, Jones's power to reject at .05 was .18 whereas Smith's power (N of 80) was .60-more than three times greater. (pp. 1277-1278).

In sum, the implications of focusing solely on significance testing can be misleading, especially in biomedical research where underpowered studies are not uncommon. In the meta-analytic approach, the focus is on effect sizes, which is not influenced by sample size relative to significance testing (Rosenthal, 1995). Therefore, by using effect size statistics, the purpose of the current study is to better establish the efficacy and safety of antidepressants therapeutic effect in PD. Moreover, by a conducting a meta-analysis of this literature, future research can use the effect size results obtained from this study to calculate statistical power.

The meta-analysis that is being conducted as a dissertation will significantly contribute to the study and treatment of depression in PD. If this meta-analysis reveals that antidepressants have a positive and significant effect on physical (i.e., motor

disability) and psychological (i.e., depression and cognitive function) health on PD patients (both depressed and non-depressed), this finding might translate into a greater percentage of depressed patients being actively treated by their physicians. Alternatively, if the study reveals that PD patients develop side effects (see Table 3) or do not benefit from taking antidepressants (as evidenced by small and non-significant effect sizes), this finding could also lead to the prevention of added suffering for patients seeking treatment for affective disturbances. Thus, irrespective of whether positive or negative effect size results are obtained, it is clear that this study has the potential to have a major impact on how PD patients are treated for depression within the clinical care setting.

Interestingly, another meta-analysis had recently been conducted and suggested that antidepressants were not effective in treating PD-related depression (Weintraub et al., 2005). However, one problem with the other meta-analysis is that it calculated effect size statistics by combining open-labeled and placebo-controlled trials. Therefore, the other meta-analysis can be criticized for mixing together experimentally good and bad studies. The inclusion of studies with high experimental control is important to ensure internal and construct validity of the effect size data. This criticism is known as the "garbage in and garbage out" issue and can bias the conclusions drawn from meta-analytic data (Fiske, Schacter, & Zahn-Waxler, 2001). Because the present meta-analysis will only include studies that used placebo-controlled trials, the basic threats to internal validity (e.g., maturation, regression to the mean, and placebo effects) will be more adequately controlled and increase the validity of our findings. Furthermore, the present meta-analysis will potentially have greater reliability than quantitative reviews (e.g., Ives et al., 2004; Klaassen et al., 1995; Poewe & Seppi, 2001; Weintraub et al., 2005) of this

literature because antidepressants effects will be examined on a comprehensive range of patients (depressed and non-depressed; early through late PD) and outcomes (physical and psychological). Taken together, this study will be the first to determine systematically the magnitude and significance of the therapeutic effect of antidepressants in all PD patients and from placebo-controlled trials.

Methods

Literature Search

To conduct the proposed meta-analysis, three strategies were used to obtain eligible research reports. First, a computerized search was made using *PsycInfo*, *PUBMED, Dissertation Abstracts Online*, *Nursing & Allied Health*, and the *Health Periodicals Database*. Various keyword permutations, such as PD and antidepressants, PD and depression, PD and mood, PD and affective disorders, PD and therapy, and PD and drugs, were used when searching through the computerized databases. Additionally, all antidepressant drugs (e.g., selegiline, reboxetine, and imipramine) were used as key terms in the various databases.

A second approach to obtain eligible research reports was to examine citations within reports that were identified and subsequently retrieved and screened for eligibility (e.g., Ives et al., 2004). It should also be noted that the procedures for generating this bibliography included no restrictions according to type of report or nature of publication. Thus, books, technical reports, conference papers, and dissertations, as well as published journal articles, were included.

Finally, to acquire non-published work, authors of published studies were contacted via e-mail and asked to supply information on any non-published papers that

they may have on antidepressants in depressed or non-depressed PD patients. Furthermore, all conference proceedings related to movement disorders, neurology, neuropsychology, psychology, psychiatry, and medicine were examined for unpublished work. Altogether 93 authors from a combination of published studies and unpublished abstracts within conference proceedings were contacted.

Overall, 60% of these authors have responded to inquiries about non-published work relating to antidepressants in PD. However, from the authors that did respond, 1 (Chung & Nutt, 2004) out of 2 (Chung & Nutt, 2004; Palhagen, 2004) identified unpublished studies was obtained and met the inclusion criteria for this study. For the remaining 40% of authors that did not respond to the initial inquiry, these authors were solicited for unpublished data through e-mail and hand-written letters. Unfortunately, these attempts did not increase the percentage of responses. Nonetheless, the procedures used to obtain published and unpublished studies were adequate to conclude that the "file drawer" will not be problem for this meta-analysis.

Inclusion Criteria

To be included in the meta-analysis, studies had to meet each of the following conditions: 1) The study had to have been placebo-controlled, have been wait-list controlled, or have involved a no-treatment control group. However, the control group must not have received another antidepressant for comparison. 2) For pragmatic reasons, the study had to be written in the English language. 3) The patients examined in the study had to suffer from Parkinson's disease and not from a related movement disorder (e.g., essential tremor or myasthenia gravis). 4) The study had to possess quantitative data from which an effect size could be computed. 5) The study had to involve a proper

antidepressant drug. Thus, for instance, the possible antidepressant effects of levodopa were ignored because the drug was developed specifically for the treatment of PD motor symptoms. Moreover, the evidence has shown that levodopa is ineffective at alleviating depression in PD (Cheifetz, Garron, Leavitt, Klavans, & Garvin, 1971; Goodwin, Murphey, Brodie, & Buney, 1970; Hoehn et al., 1976; Lesser et al., 1979; Marsh & Markhan, 1973; Mayeux et al., 1981; Morrison, Borod, Brin, Halbig, & Olanow, 2004). However, because there is evidence that selegiline may reduce depression (Allain et al., 1991; Allain et al., 1993; Quitkin et al., 1984; Mann & Gershon, 1980) and improve motor function (Parkinson Study Group, 1993) at lower doses (5 to 20 mg daily), then all studies using this drug were included for the present analysis.

Materials

A literature search from the various databases has resulted in 43 published and one unpublished article that have met the above inclusion criteria. Their general characteristics include: 1) four studies that used TCAs; 2) five studies that used SSRIs; and 3) 35 studies that used MAOIs in PD samples. In the TCA studies, all four examined depression as a health outcome while using PD patients suffering with depressive symptoms that ranged from mild to severe depression. In the SSRI studies, 4 out of the 5 examined depression as a health outcome while using depressed PD patients as a clinical population. One other study looked at changes on physical health outcomes (and not depression) for non-depressed PD patients.

Finally, in the MAOI studies, seven examined depression as a health outcome in PD patients with mild depressive symptoms. Six separate studies examined changes in cognitive functioning only for non-depressed PD patients. Twenty-three studies examined

changes in physical health outcomes for nondepressed PD patients. All of the studies used selegiline as the MAO-I of choice because of its potential to improve depression, cognition, and parkinsonian symptoms at the same time.

Statistical Analysis Plan

Extrapolating Effect Sizes. The effect size statistic used in this meta-analysis was Cohen's effect size (*d*). Cohen's (*d*) represents the standardized mean difference between treatment and control groups measured in standard deviation units (Hedges, 1981). The majority of transformations and analyses were performed using the software DSTAT (Johnson, 1990). Transformations and analyses not performed by the software were performed following the procedures described in Glass, McGraw, and Smith (1981). When there were insufficient data from which to calculate *d*-values but an effect was noted as non-significant, the effect size was coded as zero, taking the conservative approach (Rosenthal, 1984).

Cohen's *d*-value was computed in two manners in the present meta-analysis. First, an overall effect size was computed for each study (see Table 1). Secondly, one effect size was computed for each specific outcome type examined (discussed below), averaged across all outcomes within outcome type and within study. Additionally, the corresponding correlation coefficient (*r*) was computed for each *d*-value (see Table 1).

Evaluating Effect Sizes. To evaluate effect sizes, outcomes were averaged within each study and across all studies to determine the magnitude and significance of the overall mean weighted effect size (see Table 1). Moreover, all effect size magnitudes within this meta-analysis were assessed according to the effect size index established by Cohen (1977, 1988). Thus, for the standardized mean difference, ES < .20 is negligible,

ES $\geq$ .20 is considered small, ES $\geq$ .50 is considered medium, and ES $\geq$ .80 is considered large (Cohen, 1977, 1988). The analogous values for the correlation effect size are r $\geq$ .10 (small), r $\geq$ .25 (medium), and r $\geq$ .40 (large). Additionally, contrasts among the group means were performed according to Hedges and Olkin (1985), with the ensuing *Qb* evaluated against a χ^2 distribution.

Moderating Variables. To test for moderating variables, a test of homogeneity of variance was conducted (Rosenthal, 1995). However, even if the test was non-significant, several planned contrasts were conducted to better understand the research literature (Rosenthal & DiMatteo, 2001).

The first planned contrast separately examined the efficacy and safety of antidepressants. First the overall mean weighted effect size was compared between outcomes and side effects (see Tables 2 & 3). A health-outcome was operationalized as any health related measure that the researcher(s) hypothesized to improve (a priori) while being on antidepressants. It should be stated that the dependent measure was operationalized as a health outcome even if the treatment effect did not support the initial hypothesis of the researcher(s) and favored the placebo groups. In this case, the health outcome was coded as a negative effect size and not a side effect. A side-effect was operationalized as any adverse event that was recorded on a post-hoc basis and was not a part of the central aims/hypotheses of the study. Side-effects were operationalized in this manner because no studies were designed, of course, to test a priori whether PD patients would become ill as a function of antidepressant medication. Accordingly, if a greater percentage of placebo patients reported fewer adverse events relative to the antidepressant group, then the data would have been coded as a negative effect size.

Alternatively, the data would have been coded as a positive effect size if fewer adverse events were observed for the antidepressant relative to the control group. Thus, effect sizes were coded as positive on health outcomes and side effects when the treatment effects favored the antidepressant group.

Overall, it was predicted that health outcomes would be positively and significantly different from zero. While side effects may produce several negative effect size results, it was predicted that it would not be significantly different from zero. Moreover, it was predicted that the planned contrast would be significant and in favor of health outcomes. Together, these results would provide evidence that antidepressants are overall safe and effective.

While antidepressants may be effective in increasing health outcomes, it would be interesting to examine whether their efficacy is greater on physical or psychological health. Therefore, the second planned contrast was on the effects of antidepressants across the type of health outcome measured in each study. The outcome types that were compared were physical (see Table 4) and psychological health (see Table 5). It was predicted that the overall mean weighted effect size for both physical and psychological health outcomes would be significantly different from zero. However, it was not clear whether a planned contrast would show that antidepressants significantly improved one health outcome over another. Therefore, by examining this moderator in the present meta-analysis, I would be able to provide more information on the efficacy of antidepressants on specific health outcomes.

In addition to examining the effects of all antidepressants on physical and psychological health outcomes, another important moderating variable is the effect of

type of antidepressant class (i.e., TCA vs. SSRI vs. MAOI) on all outcomes (health outcomes and side effects). Once again, it was predicted that the overall mean weighted effect size for TCAs, SSRIs, and MAOIs would be significantly different from zero (see Tables 6-8). However, it was not clear whether a planned contrast would reveal that one specific antidepressant class would produce a significantly greater mean weighted effect size over another antidepressant class. The analysis on this moderating variable has the potential to help clinicians decide which antidepressants are the most beneficial for their PD patients.

To help clinicians further determine the type of antidepressant to be used on their PD patients, a separate planned contrast was conducted between health outcomes and side effects within each drug class (see Tables 9-14). In reiteration, a health outcome was operationalized as any health related measure that the researcher(s) hypothesized to improve (a priori) while being on antidepressants. A side-effect was operationalized as any adverse events that was recorded on a post-hoc basis and were not part of the central aims/hypotheses of study. Thus, the overall mean weighted effect size was calculated for health outcomes and side effects separately within each drug class (i.e., TCAs, SSRIs, and MAOB-Is) to determine if they were significantly differ from zero. Then, a planned contrast was conducted between health outcomes and side effects for each antidepressant class in order to establish the safety and efficacy of TCAs, SSRIs, and the MAO-B inhibitor selegiline.

It should be added that all of the above moderators would be examined even if the overall test of homogeneity was not significant. Other moderators that will be explored if the test of homogeneity is significant are PD severity (i.e., early, middle, and late PD) and

the duration of antidepressant therapy (i.e., short term vs. long-term). Moreover, the differences between L-dopa and non-L-dopa treated patients will be assessed as a possible moderating variable within these studies.

Finally, a sub-analysis was conducted for the studies that examined the effects of antidepressants on depression only as a health outcome. This analysis will be able to provide meaningful information on whether or not antidepressants can actually reduce depression in PD. Once again, the overall mean weighted effect size was calculated using the procedures outlined above, and the overall effect size was evaluated according to the effect size index established by Cohen (1977, 1988). The severity of depression and antidepressant class used within each study would also be explored as potential moderating variables.

Results

Overall Effects

The characteristics for each study and their associated effect sizes are shown in Table 1. The mean weighted effect size across 45 studies which contained 5,539 PD patients and 632 effect sizes, produced a negligible (d = .13; r = .06), yet significant ($p <$ .001), treatment effect. The fail safe K for this meta-analysis was 53 (Orwin, 1983), which makes it unlikely that the overall results would be altered by unretrieved studies.

Although the overall effect size for this analysis was significant, the strength of a meta-analysis relies in the ability to test for homogeneity of variance to determine whether there are any moderator variables that may account for the variance (Rosenthal, 1995). The test for homogeneity was found to be nonsignificant (Qw = 54.19, p = .14), indicating that the observed variance may primarily be a result of sampling error and not

of moderating variables. However, because there were small subject samples used within many of the studies in this meta-analysis, it is possible that the *Q*-test did not have the statistical power to reject homogeneity. As a result, a planned contrast was conducted for the moderating variables that were discussed previously to understand the research literature better (Rosenthal & DiMatteo, 2001).

Moderators

Health outcomes versus Side Effects. As noted in Table 2, the overall mean weighted effect size for studies assessing health outcomes was $d = .28$ and was significantly different from zero ($p = .001$). As significant within-group effect size variation ($Qw = 15.79$, $p < .05$) existed in the overall aggregate analysis (see Table 2), comparisons were made among all significant health outcomes (i.e., neurological outcome/ status/ health, pain, depression, subjective evaluation of medications, and global psychological function).

Neurological outcomes were first compared with all other significant health outcomes from Table 2. When neurological outcomes were compared with pain outcomes there was a significant difference, $Qb\ (1) = 32.11$, $p < .01$, indicating that the mean weighted effect size was stronger for pain ($d = 1.78$) than neurological outcomes ($d = .26$). However, the difference between neurological ($d = .26$) and depression ($d = .25$) outcomes was not significant, Qb(1)= 3.00, ns. The difference between neurological ($d = .26$) and subjective evaluation of medications ($d = .88$) was also significant, Qb(1) = 26.16, $p < .01$. Finally, neurological and global psychological outcomes were compared. The difference was significant, $Qb(1) = 33.58$, $p < .01$, indicating that the mean weighted

effect size was stronger for neurological (d = .26) than global psychological function (d = .22).

The mean weighted effect size for pain was compared to all other significant health outcomes (except neurological) from Table 2. Contrast among the group means showed that the mean effect size for pain (d = 1.78) was significantly higher than the one for depression (d = .25; $Qb(1) = 29.11$, $p < .01$), subjective evaluation of medications (d = .88; $Qb(1) = 9.36$, $p < .01$), and global psychological function (d = .22; $Qb(1) = 4.55$, $p < .05$).

The mean weighted effect size for depression was compared to subjective evaluation of medications and global psychological health outcomes. Contrasts among the group means showed that the mean effect size for depression (d = .25) was significantly less than PD patients' subjective evaluation of medications (d = .88), $Qb(1) = 23.16$, $p < .001$. However, contrasts showed that the mean effect size for depression was significantly greater than global psychological outcomes (d = .22), $Qb(1) = 30.58$, $p < .001$.

Finally, the mean weighted effect size for subjective evaluation of medications was compared to global psychological health outcomes. Contrasts showed that the mean effect size was significantly greater for PD patients subjective evaluation of medications (d = .88) relative to global psychological health outcomes (d = .22), $Qb(1) = 7.89$, $p < .01$.

Taken together, it appears that antidepressants were equivocally beneficial for motor and depression outcomes, while being differentially beneficial for global psychological and pain outcomes. Because positive and significant effect sizes were

obtained for these health outcomes, it is not surprising that PD patients rated their antidepressant medication (i.e., subjective evaluation of medications) as having a beneficial effect on their health.

In terms of side effects (see Table 3), antidepressants produced only marginal adverse events on health where d = -.08, and was not significantly different from zero (p = .09). A comparison was made between health outcomes (see Table 2) and side effects (see Table 3). Contrasts among the group means showed that the mean effect size for health outcomes (d = .28) was significantly higher than the one for side effects (d = -.08), Qb(1) = 35.48, p < .001. Thus, it appears that the data from this meta-analysis show that antidepressants are overall safe and provide salutary health benefits to PD patients.

Physical versus Psychological Outcomes. While the above results provide evidence on the salutary health benefits for antidepressants in PD, one moderating variable is the difference between physical and psychological health. As noted in Table 4, the overall mean weighted effect size for studies assessing physical health outcomes was d = .45 (95% CI= .13/.52) and was significantly different from zero (p = .03). In terms of psychological health outcomes (Table 5), antidepressants also produced a positive and significant effect size result where d = .26 (95% CI= .06/.42) and was significantly different from zero (p = .02). Contrasts among the group means indicated that the mean effect size for physical health outcomes was significantly higher than the one for psychological health outcomes, Qb(1) = 39.16, p < .001.

Overall Effects by Drug Class. Although the previous results provide an index for the efficacy and safety of antidepressants as a whole, it is more worthwhile to examine these effects for each specific drug class (i.e., TCAS, SSRIs, and MAOIs). The analysis

of this moderating variable can help clinicians to decide which antidepressants are most beneficial for their PD patient.

Looking at Table 6, the overall mean weighted effect size for studies using TCAs was d = .42 (95% CI = .07 /.78) and found to be significantly different from zero (p = .01). In terms of studies using SSRIs (see Table 7), the overall mean weighted effect size was d = .53 (95% CI= .16/.91), and was significant from zero (p <.01). The results from studies using MAOIs (see Table 8) only revealed a modest improvement on health outcomes (d = .11, 95% CI= .05/.16) but was also significant from zero (p < .001). Contrasts among the group means revealed that the overall mean weighted effect sizes for the three type of drug classes were significantly different from each other, $Qb(2) = 10.45$, $p < .05$. However, a contrast revealed that the mean weighted effect size between SSRIs and TCAs was not significant, Qb(1) = .84, *ns*. Together, these results indicate that the overall mean effect size was strongest for SSRIs and TCAs compared to MAOIs in PD patients.

Health Outcomes and Side Effects by Drug Class

While the previous results show that the overall mean weighted effect size varies as a function of antidepressant class, it is important to examine where these effects occurred. More specifically, what role does each health outcome and side effect play on the overall positive and significant mean effect size results observed from the above analyses (see Tables 6-8). Therefore, effect sizes were computed on health outcomes and side effects for TCAs, SSRIs, and MAOIs separately.

Health Outcomes versus Side Effects for TCAs. Table 9 shows that the overall mean weighted effect size on all health outcomes was robust (i.e., d = .68) and

significantly different from zero ($p < .01$). In terms of side effects (see Table 10), TCAs produced a small negative effect size result where $d = -.27$ and was also significantly different from zero ($p < .05$). However, a planned contrast between the group means revealed that the overall difference between health outcomes and side effects was significant ($Qb = 42.2$, $p < .001$). Together, these results on TCAs suggest that the health benefits produced by TCAs outweigh their risks. However, the small but significant effect size result obtained from side effects (i.e., $d = -.27$, $p < .05$) negatively impacts the overall mean weighted effect size result (i.e., $d = .42$) obtained from studies using this class of antidepressants (see Table 6).

Health Outcomes versus Side Effects for SSRIs. Looking at Table 11, the overall mean weighted effect size on all health outcomes for SSRIs was $d = .36$, and significantly different from zero ($p < .001$). While SSRIs produced a smaller mean weighted effect size for health outcomes relative to TCAs (i.e., $d = .68$), it should be noted that SSRIs were not as risky for PD patients (see Table 12). More specifically, SSRIs produced an effect size result that was close to zero on side effects (i.e., $d = -.002$). Furthermore, a planned contrast for the group means between health outcomes and side effects was significant, $Qb(1) = 52.31$, $p < .001$. Together, these results suggest that SSRIs are safe and produce salutary health benefits for PD patients.

Interestingly, the results from two other meta-analyses have shown SSRIs to be better tolerated and more effective in treating depression in elderly adults relative to TCAs (Wilson, Mottram, Sivanranthan, & Nightingale, 2001; Wilson & Mottram, 2004). However, the results from this meta-analysis only partially coincide with the previous meta-analyses in that SSRIs were found to be safe but not effective in treating depression

for PD patients. Moreover, it was observed that TCAs produced greater salutary health benefits (i.e., d = .68) for PD patients relative to SSRIs (i.e., d = .36). Therefore, TCAs might offer a more positive alternative to SSRIs for the improvement of health related quality of life in PD patients.

Health Outcomes versus Side Effects for MAOIs. Looking at Table 13, the overall mean weighted effect size on all health outcomes for MAOIs was d = .20 and was significantly different from zero (p = .001). Similar to SSRIs, a negligible and nonsignificant effect size emerged on side effects (see Table 14) when PD patients were given MAOIs (d = -.07, *ns*). A planned contrast between the group means of health outcomes and side effects was significant, $Qb(1) = 48.07$, $p < .001$. Together, these results suggest that MAOIs can provide modest health benefits to PD patients without a significant risk of side effects. Most importantly, the effect size magnitude obtained from this meta-analysis supports previous research indicating that selegiline (10 mg a day) does not increase the risk of mortality in PD patients (Thorogood et al., 1998).

Antidepressants on Depression Outcomes

The data from the above analyses suggest that antidepressants can improve health outcomes for PD patients while producing only mild side effects. However, before concluding that antidepressants are efficacious, their effects have to be methodically examined on depression outcomes. As a result, a sub-analysis was conducted to further determine the efficacy of antidepressants in treating PD related depression. Overall, the mean weighted effect size across all studies (k= 18) assessing the effects of antidepressants on depression was d = .25 (r = .12) and was significant from zero (p < .01). The fail safe K for this sub-analysis was 25 (Orwin, 1983). Because the test of

homogeneity was significant (Qw = 37.37, p = .003), a stem-and-leaf plot was conducted to examine the central tendency, variability, and normality of the effect size distribution (Lipsey & Wilson, 2001).

Table 15 indicates that the effect sizes ranged from -.2 to 2.00, but the model interval for effect sizes was in the .00 range. In spite of the overall mean weighted effect size being modestly positive and significant, the stem-and-leaf display suggests that antidepressants may not be effective at reducing depression in PD. One explanation for the discrepancy between the aggregate analysis and stem-and-leaf plot was that the mean weighted effect size (i.e., d = .25) may have been inflated by the presence of outliers. Alternatively, the significant test of homogeneity observed from the aggregate analysis could have been influenced by the presence of moderating variables (e.g., study characteristics). For instance, an examination of the studies within the stem-and-leaf plot does reveal variability as a function of antidepressant class.

An examination of effect sizes from Table 15 indicates that the majority of studies found in the zero effect size range (i.e., -.09 to .09) used selegiline at a dose (10 mg a day) where it was acting as an MAOI-B inhibitor (i.e., 10 out of 15 studies). Consider that selegiline generally produces its maximal antidepressant effects at slightly higher doses (20 mg a day), when it is influencing MAOI-A inhibition (Quitkin et al., 1984; Mann et al., 1989). Therefore, it appears that the stem-and-leaf plot was centered at zero because many of the effect sizes derived from studies which used a less efficacious antidepressant dose of selegiline (i.e., 10 mg per day). To support this notion further, the effect sizes found in the upper intervals of the stem-and-leaf plot (see Table 15) derive primarily from studies which used antidepressants that can effectively influence serotonin

and norepinephrine brain levels (i.e., TCAs and SSRIs). Based on this observed variability, each antidepressant class was examined as a potential moderating variable on depression outcomes.

TCAs and Depression. The results from a sub-analysis on TCAs produced a robust treatment effect for depression in PD where d = .55 (SE = .18; 95% CI = .19 / .90) and was significant from zero (p = .01). Furthermore, the distribution of effect sizes were homogeneous (Qw = 5.98, p = .11), indicating that any variability found in the effect size data was likely due to sampling error and not study characteristics or outliers (Lipsey & Wilson, 2001). While it can be concluded that TCAs were effective at treating PD related depression, it is important to note that the 95% confidence interval had a wide distribution around the population mean.

The observed variability found in the TCA effect size results can not be attributed to dosing since most of the studies used the appropriate amount of medication for a geriatric population. For instance, the studies in this meta-analysis used amitriptyline (25 mg daily), imipramine (150-200 mg daily), desipramine (100 mg daily), and nortriptyline (25-150 mg daily). Maxmen and Ward (1995) present a range of doses that should be used on geriatric patients with these TCAs: amitriptyline (25-100 mg daily), imipramine (30-100 mg daily), desipramine (20-100 mg daily), and nortriptyline (10-75 mg daily). Because only one study used a TCA at its lowest therapeutic dose (Indacco & Carrieri, 1988), then some other factor might be contributing to the large 95% confidence interval observed in this meta-analysis—namely, methodological quality.

Klassen et al. (1995) conducted a signed test meta-analysis to obtain studies on the effects of antidepressants on PD patients. Although their study did not use effect size

statistics to examine the efficacy and safety of antidepressants, their meta-analysis did rate the methodological quality of each study. Briefly, the researchers used a list of 46 criteria concerning methodological aspects of research (e.g., study population, interventions, measurement of effect, and data presentation / analysis) and then aggregated the scores of each criterion to obtain a total score for each study. The total maximum score could range from 0 to 100, with higher scores indicating higher methodological quality. Overall, the four TCA studies which were included within the present meta-analysis were rated as poor quality (Klassen et al., 1995). For instance, the researchers rated the Strang (1965) and Laitinen (1969) studies with a total maximum score of 37 out of 100. Additionally, the Anderson et al. (1980) only obtained a total maximum score of 41. However, the Indaco and Carrieri (1988) study faired a little better with a total maximum score of 57 out of 100. Taken together, the results from the present meta-analysis do not allow for a definitive conclusion on the efficacy of TCAs on PD related depression.

SSRIs and Depression. The results from SSRIs initially produced robust improvements for depression outcomes in PD patients where d = .58 (95% CI = .33 / .82) and was significant from zero (p < 001). However, this sample of effect sizes was also significantly heterogeneous (Qw = 14.34, p = .00). As a result, a stem-and-leaf plot was conducted to examine the central tendency, variability, and normality of this effect size distribution (Lipsey & Wilson, 2001). Looking at Table 16, it could be observed that 3 effect size results were more than 3 standard errors (SE = .12) away from the grand mean (i.e., d = .58). Consequently, these 3 effect sizes were treated as outliers.

One common procedure for handling outliers is to eliminate/trim them from the effect size distribution (Lipsey & Wilson, 2001). Therefore, another aggregate analysis was conducted for SSRIs on depression outcomes by removing the three extreme effect size results (i.e., *d* = 1.3, 1.9, 2.2) that were observed from Table 16. Overall, the results from the trimmed analysis revealed that the mean weighted effect size was only modestly positive *d* = .17 (95% CI= -.12 / .45) and no longer significant from zero (*p* = .12). Moreover, the sample of effect sizes was homogenous (*Qw* = 2.72, *p* = .91) once the three outliers were removed. Consequently, another analysis was conducted with the inclusion of the smallest outlier effect size (*d* = 1.3) in the distribution. The overall mean weighted effect size for SSRIs on depression marginally increased (*d* = .21), and a trend towards significance was observed (*p* = .08). Additionally, the sample of effect sizes remained homogenous (*Qw* = 4.65, p= .80). The effect size distribution was no longer homogenous (Qw = 21.28, *p* = .01) when the next outlier (i.e., *d* = 1.9) w*a*s included in the trimmed analysis.

Because the previous analysis revealed that outliers were present within the SSRI literature then it is logical to assume that these outliers (i.e., *d* = 1.9 and 2.2) would have inflated the overall mean weighted effect size on depression scores. Therefore, it is necessary to reanalyze the overall effect size data on depression outcomes. After removing/trimming the identified outliers from above, the mean weighted effect size changed from *d* = .25 to *d* = .11. Furthermore, the test of homogeneity on overall depression was no longer significant (*Qw* = 16.14, *p* = .37). Because the overall mean weighed effect size for depression had changed as a result of the trimmed analysis, all previous tables using this outcome were adjusted with the new trimmed depression effect

size result. Consequently, the overall mean weighted effect size results only slightly decreased for health outcomes (see Table 2), psychological health outcomes (see Table 5), and SSRI health outcomes (see Table 11).

The Practical Significance of SSRIs on Depression. Although the trimmed analysis produced a small treatment effect that was approaching statistical significance (d =.21, p = .08), the question remains as to whether or not the observed benefits with SSRIs on depression can be of practical significance within the medical field. For example, one study examined the efficacy of aspirins in preventing heart attack (Steering Committee of the Physicians' Health Study Research Group, 1989). Initially, it was observed that aspirin only produced a small treatment effect on heart attack risk relative to those individuals taking a placebo (i.e., r = .034). However, the researchers translated their effect size result with a binomial effect size display (BESD) to test the practical significance of their small effect size findings. The Physicians' Health Study Research Group (1988) estimated that their small effect size translated into a 3.4% reduction in heart attack risk for individuals taking aspirin relative to those individuals taking placebo. The researchers concluded that their small but positive effect size was of practical significance because thousands of lives would be saved by a relatively safe and inexpensive over-the-counter medication. For this reason, a meta-analyst should be concerned more about effect sizes than p-values.

Because it is also plausible that the small effect size result obtained for SSRIs on depression (i.e., d = .21; r = .11) may be of practical significance for depressed PD patients, a binomial effect size display (BESD) was conducted on a post-hoc basis. Briefly, the BESD converts any given $r_{effect\ size}$ into a success rate/percentage that is

displayed within a 2 x 2 table for any given experimental and control group (Grisson & Kim, 2005).

Looking at Table 17, the percentage of success for the SSRI antidepressant group on depression outcomes was estimated at 56% whereas the percentage of success was 44% for the placebo control group on depression. These results from the BESD can be interpreted as 12% of all depressed PD patients benefiting on depression if they were on SSRI medication over placebo (Grisson & Kim, 2005). Because approximately half of all PD patients suffer with depression (Doonief et al., 1992; Edwards et al., 2002), the 12% success rate observed from the BESD would translate into thousands of PD patients improving with their depression if they were placed on SSRI medication. Therefore, it can be concluded that the small but positive effect size observed with SSRIs on depression (i.e., d = .21, r = .11, p = .08) does have practical significance for the clinical care setting.

MAOIs and Depression. The results from a sub-analysis on studies using MAOIs produced a negligible (d = .08; 95% CI = .00 / .30), but significant (p = .02), treatment effect for depression. Because the test of homogeneity was not significant (Qw = 2.16, p = .99), any variability found in the effect size data was likely due to sampling error and not study characteristics or outliers (Lipsey & Wilson, 2001).

A BESD was also conducted on a post-hoc basis to determine the practical importance of the effect size result produced by MAOIs on depression. Looking at Table 18, the percentage of success for the MAOI antidepressant group on depression was estimated at 52% whereas the percentage of success was 48% for the placebo control group on depression. The results from the BESD can be interpreted as only 4% of all

depressed PD patients improving on their depression if they were on MAOIs (i.e., selegiline) over placebo. Thus, it appears that the significant effect size observed with MAOIs (d = .08, r = .04, p < .05) may not be of practical importance when treating PD-related depression in the clinical care setting. However, given that selegiline was not prescribed at its optimal antidepressant dose (i.e., 20 mg a day) and many of the studies used PD patients suffering with only mild depressive symptoms (see Table 19), the efficacy of MOAIs on PD-related depression cannot be concluded from this meta-analysis. However, what can be concluded from this meta-analysis is that selegline (10 mg a day) offers many salutary health benefits (see Table 13) while producing minimal side effects (see Table 14) on PD patients. Therefore, selegiline can be prescribed by physicians to improve the overall health related quality of life (e.g., neurological-motor function and global psychological function) for their non-depressed PD patient.

Comparisons Between Drug Class. Because the above analyses revealed that each antidepressant class produced different effect size results on depression outcomes, contrasts among the group means were conducted between TCAs, SSRIs (trimmed), and MAOIs. This meta-analysis found that the mean weighted effect size between TCAs (d= .55) and SSRIs (d = .21) was significant, $Qb(1) = 5.51$, p <.05. Moreover, a comparison between the mean weighted effect size of TCAs and MAOIs (d = .08) was also found significant, Qb (1) = 8.00, p <.01. Finally, the mean weighted effect size between SSRIs (d = .21) and MAOIs (d = .08) was also compared and found significant, Qb(1) = 9.33, p < .01. Together, these results suggest that TCAs can produce the largest antidepressant effects on PD patients. However, it was also observed that TCAs produced a significant negative effect size result on overall side effects (i.e., d = -.27, p < .05). For this reason,

the decision to choose between SSRI and TCAs should be carefully considered and monitored on an individual basis, weighing (and/or ranking) the benefits of improving depressive symptomatology together with the risk of creating and tolerating side effects.

Disease Severity and Depression

Another important moderating variable that can interact with the overall mean weighted effect size on depression outcomes is depression severity. As a result, the overall mean weighted effect size was computed for studies that had PD patients suffering with depressive symptoms, mild depression, moderate depression, and major depression. However, prior to computing the effect size for each category of depression severity, the identified outliers from above were removed for the present analysis.

Looking at Table 19, the results showed that PD patients suffering with major depression did benefit (d = .31, p = .02; 95% CI = .00 / .62) from taking antidepressants. Moreover, antidepressants produced a modestly positive effect size with a trend toward significance when tested on PD patients suffering with moderate depression (d = .27, p = .07; 95% CI = -.10 / .64). However, PD patients suffering with mild depression (d = .23, p = .12; 95% CI= -.15 / .60), and depressive symptoms (d = .09, p = .02; 95% CI = -.08 / .26) benefited less from taking antidepressants.

As expected, the planned contrast for the group means between PD patients suffering with depressive symptoms, mild, moderate, and major depression was significant, $Qb(3) = 14.36$, $p < .01$. The results from this meta-analysis are in line with other studies showing that patients with dysthymia or minor depression are less likely to respond to antidepressant treatment than patients with more severe depression (Ackermann & Williams, 2002; Oxman & Sengupta, 2002). Nonetheless, to further

understand the antidepressant literature, the effects of each drug class was examined as a function of depression severity. Once again, it is hoped that this analysis can help clinicians determine which antidepressants are effective in the treatment of depression for their PD patients.

When TCAs were tested on PD patients with mild depression, the overall mean weighted effect size was positive and produced a statistically significant trend (d = .33, p = .06). However, when TCAs were tested on patients suffering with major depression, the overall mean weighted effect size was large and statistically significant (d = 1.21, p = .00). Because there was only 1 study testing TCAs at the level of major depression, a between groups comparison could not be conducted. Interestingly, the opposite trend was seen with SSRIs when tested on PD patients with moderate and major depression. More specifically, when SSRIs were tested on PD patients with moderate depression, the mean weighted effect size was moderately positive and statistically significant from zero (d = .44, p = .03). However, when SSRIs were tested on PD patients with major depression, the mean weighted effect size was negligible and no longer statistically significant (d = .09, p = .30). A planned contrast between group means was statistically significant, $Qb(1) = 4.59$, $p < .05$), indicating that SSRIs were effective on PD patients with less severe forms of depression.

Finally, the MAOI selegiline, was examined as a function of depression severity. The results show that selegiline did produce a significant antidepressant effect on PD patients suffering with depressive symptoms (d = .09, p =.02). However, selegiline did not have an antidepressant effect on patients with mild depression (d= -.24, p = .61), or major depression (d = .00, p = 1.00). Because there was only 1 study testing selegiline at

the level of mild and moderate depression, the effect sizes were combined so that a between groups comparison could be conducted. As a result, a planned comparison was made between the mean weighted effect size of PD patients with depressive symptoms and the combined mean weighted effect size of selegiline tested on patients with mild and moderate depression (d = -.07, p = .39). The results of the planned comparison was not statistically significant, $Qb(1)$= .79, p > .30, indicating that selegiline was unable to produce an antidepressant effect irrespective of the PD patients severity of depressive symptoms.

Antidepressants on Motor Outcomes

Looking at Tables 9, 11, and 13, each antidepressant drug class (i.e., TCAs, SSRIs, and MAOIs) had a positive and significant effect on motor outcomes. Parenthetically, MAOIs (d = .36, p < .00) were able to produce the largest effect size result in comparison to SSRIs (d = .34, p < .05) and TCAs (d = .30, p = *.07)* on PD motor symptoms. However, the difference between SSRIs and MAOIs was not statistically significant, $Qb(1) = 2.49$, p = .10. The planned contrast between MAOIS and TCAs was significant, $Qb(1) = 6.64$, p < .01. Additionally, the planned contrast between SSRIs and TCAs was significant, $Qb(1) = 35.32$, p < .00. Taken together, the results from this meta-analysis indicate that SSRIs may not exacerbate PD motor symptoms (Ceravolo et al., 2000; Jimenez et al., 1994; Steur, 1993).

Discussion

This meta-analysis examined three issues pertaining to the efficacy and safety of antidepressants in PD. The first examined the magnitude and significance of antidepressants effects on PD related depression. The second assessed whether or not

antidepressants can provide salutary health benefits to all PD patients (depressed and non-depressed). Finally, the third issue was concerned with the side-effect profile of antidepressants in PD. To examine this issue, both quantitative and qualitative analyses were applied to studies that reported adverse events on this clinical population.

The Efficacy of Antidepressant on Depression

The results from this meta-analysis provide statistical evidence that antidepressants can reduce depression in PD when compared with placebo. The overall effect was negligible (i.e., $d = .11$, $p = .00$), but moderated by antidepressant class along with the severity of depressive symptoms.

Starting with the effects of each antidepressant class, it was observed that TCAs produced a robust treatment effect on depression ($d = .55$). The mean weighted effect size was modest for SSRIs ($d = .21$), and almost close to zero for the MAOI selegeline ($d = .08$). These results contradict other data showing that SSRIs have a greater therapeutic index than TCAs and MAOIs in depressed individuals without PD (MacGillivray et al., 2003; Wilson, Mottram, Sivanranthan, Nightingale, 2001). It is worth noting that the TCA literature is much older than the SSRI literature. Because older studies tend to use less experimental rigor, the effect size data for TCAs may have been positively biased. Nonetheless, the overall mean weighted effect size for SSRIs just failed to reach statistical significance (i.e., $p = .08$). Furthermore, when examining the effects of each antidepressant class as a function of depression severity, the present meta-analysis did observe a beneficial treatment effect with SSRIs. A robust and statistically significant effect size result was obtained when SSRIs were tested on PD patients suffering with

moderate depression (i.e., $d = .44$, $p = .03$), but not major depression (i.e., $d = .09$, $p = .30$).

One explanation as to why SSRIs were ineffective on severely depressed PD patients can be attributed to their having an atypical form of depression relative to other PD patients (Cummings, 1992). More specifically, severely depressed PD patients may represent a subtype of the disorder that is too neurological impaired to receive benefits from any antidepressant treatment. However, it should be noted that a large treatment effect was observed when TCAs were tested on a sample of severely depressed PD patients (i.e., $d = 1.21$, $p = .00$). Therefore, it seems unlikely that severe depression is atypical in PD. Moreover, a close examination of the two SSRI studies reveals the presence of a strong placebo effect (Leentjens et al., 2003; Wermuth et al., 1998).

Leentjens et al. (2003) observed that 50% of patients on the SSRI citalopram and 67% of patients on placebo showed significant reductions in depression from baseline to the posttest periods, but there were no significant differences between the two groups. One explanation for the observed placebo effect within this study can be attributed to sampling error because the study was terminated early due to difficulties in obtaining subjects. In total, the SSRI study contained only 12 severely depressed PD patients. Consequently, it is possible that the subjects within the Leentjens' study had characteristics (e.g., greater motivation) that are not usually found in severely depressed PD patients. These characteristics may explain why all PD patients improved on their depression irrespective of receiving placebo or the active pharmacological agent.

Wermuth et al. (1998) similarly observed that depressed PD patients in the citalopram and placebo groups improved on their depression from baseline to the posttest

periods, but there were no significant group differences. Once again, the observed placebo effect within this SSRI study can be attributed to sampling error because the researchers wanted to test SSRIs on a sample of severely depressed PD patients. Instead, the researchers discovered that approximately 60% of their sample consisted of patients with severe recurrent brief depression (RBD), which lasted for 2-3 days. Therefore, a treatment effect was not observed from Wermuth's study because depression would have subsided in the majority of PD patients after several days. All things considered, the placebo effect observed within the SSRI studies can not generalize to severely depressed PD patients. As a result, the effectiveness of SSRIs on severe depression in PD has yet to be established.

Interestingly, the results from the present meta-analysis do not coincide with the meta-analysis conducted by Weintraub et al. (2005). Briefly, the researchers examined the effects of antidepressants on PD-related depression and obtained a large effect size on depression outcomes for the antidepressant group (i.e., d = 1.34) and the placebo control group (i.e., d = 1.19). However, the researchers did not observe a significant between group difference, $Qb(1)= .43$, $p = .51$. Consequently, the researchers concluded, "that antidepressant treatment has a very large, but non-specific, positive effect on depression in PD." Regrettably, their conclusion that antidepressants have a "non-specific" therapeutic effect may be flawed because the effect size data from their control group derived from the two SSRI studies that were identified here as suffering with sampling error (i.e, Leentjens et al., 2003; Wermuth et al., 1998). Moreover, the researchers excluded an entire antidepressant class from their analysis (i.e., TCAs), which in turn

further limited their ability to detect a significant treatment effect between the antidepressant and placebo group.

Weintraub et al. (2005) excluded studies that did not use a standardized rating scale of depression severity. Because the TCA studies did not utilize standardized instruments for assessing depression, the researchers excluded an entire antidepressant class from their analysis. In contrast, the present meta-analysis only required that each study utilize a dependent measure that provided qualitative data to be coded into an effect size statistic. However, it should be noted that there are no standardized instruments for measuring depression in PD (Leentjens, Verhey, Luijckx, & Troost, 2000). For this reason, TCA studies were included into the present meta-analysis and served as an important moderator on depression outcomes (d = .55) in PD. However, the present meta-analysis can be criticized for including studies that may have been confounded by measurement error.

Selegiline was also examined as a function of depression severity. The results showed that selegiline produced a negligible but significant effect size result on PD patients with depressive symptoms (d = .09, p = .02). Nonetheless, this effect size did not translate into a beneficial treatment effect because it was not significantly larger (i.e., Qb (1) = .79, p > .30) than the combined effect size for mildly and moderately depressed PD patients (d = -.07, p = .39).

One reason that the mean weighed effect size was significant on overall depression (d = .08, p =.02) and on patients suffering with depressive symptoms (d = .09, p = .02), can be attributed to several studies having extremely large sample sizes. For instance, 30% of the MAOI studies contained sample sizes with over 200 PD patients in

both the placebo and drug treatment groups. However, the remaining 70% of studies only contained an average of 30 subjects in the placebo group and 38 subjects in the selegeline group. While sample size may not influence the overall mean effect size for the distribution, it can have a positive effect on the *p*-value. More specifically, as the sample size increases within an effect size distribution, the sample variance will also decrease. As a result, the standard error will get smaller and it will become easier to declare an effect size as statistically significant.

To test the above assumption, a post-hoc analysis was conducted by replacing the large sample sizes from the 30% of MAOI studies with the average sample size from their respective distributions (i.e., 30 and 38 subjects, respectively). The post-hoc analysis revealed that the mean weighted effect size was no longer significant for MAOIs on overall depression ($d = .08$, $p = .15$) and on patients with depressive symptoms ($d = .09$, $p = .15$). Moreover, when the mean effect sizes were no longer weighted against the sample size of their respective distributions, the magnitude of selegeline's antidepressant effects on overall depression and patients suffering with depressive symptoms was closer to zero (i.e., $d = .03$). Taken together, these results indicate that selegeline (10 mg / daily) may not be efficacious in treating PD-related depression.

Although it can be concluded from the effect size and *p*-value data that selegeline does not produce an antidepressant effect, it should be noted that 80% of the studies were tested on PD patients that were not depressed. Since the MAO-B inhibitor was tested on an outcome (i.e., depression) where there would be little opportunity for improvement, it is not hard to imagine why the standardized mean difference between the treatment and control group would be close to zero. Thus, it is possible to attribute the small effect size

results to an effective range problem (i.e., the ceiling effect) — namely, there was little potential for variability of the effect size data because depression scores were already low at baseline. For this reason, more research needs to be conducted before concluding that selegiline (10 mg daily) is efficacious as an antidepressant in PD patients.

All in all, a positive and significant effect (d = .11, p = .00) did emerge from studies using placebo-controlled trials. Furthermore, it was determined that the significant treatment effect was moderated by TCA antidepressants overall, and SSRIs when tested on moderately depressed PD patients. Nonetheless, it is hoped that future efficacy research continues to test the effects of antidepressants on PD patients with a wider range of medication classes (i.e., NSSRIs) and on a multitude of depressed patients. Only then would it be possible to understand fully whether or not depressed PD may clinically improve with antidepressant treatment.

The Efficacy of Antidepressants on Health Outcomes

In addition to assessing the effects of antidepressants on depression outcomes, the present meta-analysis was also concerned with the efficacy of antidepressants in providing salutary health benefits in general to PD patients. Overall, the results from this analysis revealed that antidepressants were able to significantly improve motor functioning, pain, global psychological functioning, and the overall health related quality of life for PD patients (see Table 2). In addition to the overall composite analysis, it was also observed that health-outcomes were differentially affected by each antidepressant class (see Tables 9, 11, and 13).

TCAs and Health Outcomes. The results from this meta-analysis revealed that TCAs produced a modestly positive effect size with a trend towards statistical

significance (d = .30, p = .07) on neurological-motor outcomes. These results were anticipated given that norepinephrine and dopamine have been related to better motor functioning in PD (Cummings, 1992; Srinivassan & Schmidt, 2004; Srinivasan & Schmidt, 2003). Therefore, it can be concluded from this meta-analysis that TCAs provide antidepressant and antiparkinsonian benefits for this neurological population.

The present meta-analysis also observed a large treatment effect (d = 1.79) with TCAs (25 mg daily of amitriptyline) on PD patients suffering with headache pain (Indaco et al., 1988). Interestingly, the researchers found that the improvements on headache pain did not correlate with improvements on depression (Indaco et al., 1988). This observation suggests that headache pain might be related to the underlying pathophysiology of PD rather than psychosomatic processes such as stress. Interestingly, there is evidence relating headache pain in PD to reduced dopamine. It has been observed that alterations in dopamine metabolism can affect the analgesic response to periaqueductal gray matter stimulation (Akil & Liebeskind, 1975), morphine administration (VanderWende & Spoerlein, 1973), and acupuncture (Cheng & Pomeranz, 1982).

Amitriptyline can influence dopamine metabolism indirectly by blocking the reuptake of norepinephrine in the locus ceoruleus (Srinivassan & Schmidt, 2004; Srinivasan & Schmidt, 2003). However, it should be noted that antiparkinsonian medications (i.e., levodopa) which facilitate the release of dopamine have been unsuccessful in treating pain in PD (Snider, Fahn, Isgren, & Cote, 1976). Thus, it is not clear how amitriptyline increases the pain threshold in PD. Nonetheless, what is clear from the present meta-analysis is that the TCA can provide analgesic benefits for the many PD patients that suffer with severe headache pain. Because it has been estimated

that 35% of all PD patients suffer with severe headache pain (Indo, Naito, & Sobue, 1983), then amitriptyline can improve the health-related quality of life for this clinical population.

Unfortunately, the effect of TCAs on health-related quality of life was not examined within the PD literature. However, the health outcomes that were tested within the TCA literature are also the same health dimensions that are found in the common PD health-related quality of life scales (e.g., PDQ-39 and PDQL). For instance, the PDQL is a PD specific scale which examines parkinsonian symptoms (e.g., motor function), systemic symptoms (e.g., pain), emotional functioning (e.g., depression and general psychopathology), and social functioning. Because a positive treatment effect was observed on motor function (d = .30), pain (d = 1.79), depression (d = .55), and global psychological function (d = .81), it is logical to infer that TCAs did improve the health-related quality of life of PD patients. Therefore, it is not surprising that PD patients from the TCA studies positively (d = 1.02) evaluated their antidepressant medication.

SSRIs and Health Outcomes. In addition to assessing the efficacy of SSRIs on depression, the present meta-analysis was also concerned with their effects on PD motor symptoms. More specifically, this dissertation asked whether or not SSRIs exacerbate PD motor symptoms. The results from this study show that a modestly positive and significant effect size result (d = .34, p < .05) was obtained on neurological-motor function. Although, it appears that SSRIs may have improved PD, it is important to note that there was a large 95% confidence interval (i.e., CI = -.04 / .72). Nonetheless, the lower limit of the 95% confidence interval was close to zero and indicates that SSRIs do not exacerbate PD.

Although it would be easy to disaffirm the positive and significant treatment effect found with SSRIs on motor function because of the wide 95% confidence interval (i.e., CI = -.04 / .72), it is more interesting to examine whether or not the research literature can support this outcome. On this note, there is neuroanatomical evidence which shows that serotonin neurons originating from the dorsal raphe nuclei project axons to the basal ganglia (Consolazione & Cuello, 1982). There is also cellular evidence showing that serotonin influences nigrostriatal dopamine metabolism (Cobb & Abercrombie, 2003; Porras, Di Matteo, De Deurwaerdere, Esposito, & Spampinato, 2002; Porras, De Deurwaerdere, Moison, & Spampinato, 2003). Therefore, it is plausible that motor functioning can improve in PD by increasing serotonin in the dorsal raphe nuclei, which then projects and interacts with dopaminergic neurons of the basal ganlia.

Additional evidence to support the notion that the serotonin and dopamine systems interact to influence motor function can be seen in studies testing exogenous levodopa at non-dopaminergic sites (Arai, Karasawa, Geffard, Nagatus, & Nagatsu, 1994; Mura, Jackson, Manley, Young, & Groves, 1995). The efficacy of exogenous levodopa in treating the symptoms of PD can be attributed to its conversion to dopamine by the enzyme aromatic L-amino-acid decarboxylase (AADC), also known as DOPA decarboxylase (DDC). It has been observed that serotonin neurons within the rat dorsal raphe nucleus and cerebral cortex contain DDC, and is capable of catalyzing exogenous levodopa into more dopamine (Arai et al., 1994; Arai, Karasawa, & Nagatsu, 1996). Because all of the studies that were included in this meta-analysis allowed PD patients to remain on levodopa, then SSRIs may have increased dopamine and motor functioning through the moderating role of DDC within the serotonin system. All things considered,

the literature does support the notion that serotonin interacts with dopamine to influence motor function. Therefore, it is plausible for PD patients to experience motor benefits with SSRI medications.

MAOIs and Health Outcomes. The meta-analysis also provided evidence that selegeline given at a dose of 10 mg daily, can improve motor functioning in PD. More specifically, it was observed that selegiline produced a positive and significant effect size result on neurological-motor functioning (i.e., $d = .36$, $p = .00$). However, the effect size result was still modest in comparison to Cohen's effect size index (Cohen, 1977; Cohen, 1988). One reason why the overall effect size results were small is that moderators may have still been present within the distribution of neurological-motor outcomes. On this note, both the severity of PD (Early vs. Later PD) and the use of concomitant medications (selegiline alone vs. selegeline + levodopa) were examined on a post-hoc basis.

When examining the effects of disease severity as a potential moderating variable, there were 20 studies testing selegiline on early PD and 11 studies on patients with more severe PD (i.e., 10 studies on middle PD and 1 study on late PD). A two-sample t-test was conducted, and revealed no statistical difference ($t[27] = 2.05$, $p = .27$) in the effect size between early PD ($M = .39$, $SD = .27$) and later PD ($M = .27$, $SD = .29$). Therefore, the severity of PD did not have a significant impact on selegeline's treatment effectiveness on motor functioning (i.e., $d = .34$, $p = .00$).

In terms of medication usage, a two-sample t-Test was conducted, and revealed no statistical difference ($t[27] = 2.05$, $p = .86$) in the effect size between studies administering selegiline alone ($M = .34$, $SD = .30$, $K = 17$) or selegeline given concomitantly with levodopa treatment ($M = .36$, $SD = .28$, $K = 12$). Therefore, the

studies using both selegeline and levodopa together did not significantly impact the overall mean weighted effect size on neurological-motor outcomes (i.e., $d = .36$, $p = .00$).

In examining the efficacy of MAOI-B inhibitors on PD, Ives et al. (2004) concluded that selegeline reduces disability without increasing the risk of substantial side effects or the risk of mortality. Their conclusions that selegeline is safe and effective on PD concur with the present meta-analysis. However, Ives's findings are based on patients who are early in the course of their disease and had no exposure or limited exposure (less than 12 months) to levodopa treatment. The present meta-analysis differs by clearly demonstrating that selegiline improves motor functioning in moderately to severely impaired PD patients who have been exposed to levodopa treatment for several years. Therefore, it can be concluded that the findings from the present meta-analysis can generalize a larger body of patients found within the clinical care setting.

Another finding that merits consideration from this meta-analysis was the non-significant effect size result ($d = .09$, $p = .16$) produced by selegiline on the cognitive outcomes of PD patients. One explanation for why selegiline did not improve cognition in PD can possibly be attributed to an effective range problem. More specifically, selegeline was tested on PD patients that were not depressed or cognitively impaired. Therefore, it is not surprising that similar effect size values were obtained on both depression (i.e., $d = .09$) and cognitive outcomes (i.e., $d = .08$). Nonetheless, health benefits were observed with selegiline on global psychological functioning ($d = .21$, $p = .00$), and health-related quality of life ($d = .23$, $p = .00$). It is likely that selegeline improved these outcomes through its mediating effects on the primary motor pathology of PD.

All in all, the present meta-analysis demonstrates that selegeline statistical improves motor, psychological, and health-related quality of life in PD patients without cognitive impairments or depression. Although the health outcomes examined within this meta-analysis can generalize to many PD patients in the clinical care setting, the question remains as to whether the benefits seen are large enough to be of clinical/practical significance.

The Safety of Antidepressants on PD

The present meta-analysis examined the safety of antidepressants on PD by attempting to quantify and qualify the side effect experiences of these individuals from placebo controlled trials. Although prior meta-analyses have examined withdrawal rates for determining the tolerability of antidepressants (Ives et al., 2004; MacGillivray et al., 2003; Wilson & Mottram, 2004), drop-out rates were excluded from this analysis because patients may stop taking their medication for many reasons. For instance, it was observed that non-drug related adverse events (e.g., interval between clinical assessments) were positively correlated with drop out rates in older depressed patients (Wilson & Mottram, 2004). For this reason, withdrawal rates may not be a reliable index of tolerability in PD patients—namely, their age and severity of physical and psychological disability can contribute to them not taking their medication or participating in a study.

Interestingly, previous reviews have found that patients on antidepressants were less likely to withdraw from a study when they were taking SSRIs relative to TCAs. MacGillivray et al. (2003) conducted a meta-analysis on depressed adults of working age and found that patients on TCAs had an increased risk of withdrawal relative to patients receiving SSRIs. The researchers concluded that SSRIs are better tolerated than TCAs for

depressed adults in the primary care setting. Similarly, it was observed that a significantly greater percentage of depressed older adults were at risk for withdrawal when exposed to TCA relative to SSRI antidepressant treatment (Wilson & Mottram, 2004). The researchers observed that TCAs produced significantly greater gastrointestinal adverse events and neuropsychiatric side effects with TCAs relative to SSRIs (Wilson & Mottram, 2004).

The results from the present meta-analysis partially concurs with the above studies (MacGillivray et al., 2003; Wilson & Mottram, 2004). For instance, this study found that the overall mean weighted effect size for side effects produced by TCAs was modestly negative and significantly different from zero (i.e., d = -.27, p =.02). On the other hand, SSRIs produced a side effect profile that was close to zero and non-significant (i.e., d = -.002, p = .50). Therefore, on a quantitative level of analysis, the results from this meta-analysis indicate that SSRIs are more tolerable than TCAs for PD patients. However, when examining the data on a qualitative level of analysis, a more positive side effect profile emerges for TCAs.

Although, the majority of side effects produced by TCAs were negative (see Table 10), the only adverse event that was robust and significant was global psychological functioning (d = -.47, p =.03). In particular, more patients in the TCA group reported feeling drowsy relative to patients assigned to placebo group (i.e., d = -.72). It should also be noted that for cardiac/autonomic adverse events, more patients in the TCA group reported sweating as a problem relative to individuals in the placebo group (i.e., d = -.31). In terms of pain-discomfort, more patients in the TCA group reported allergic reactions than in the placebo group (i.e., d = -.37). All things

considered, it appears that TCAs did not produce substantial or life threatening side effects that would cause patients to discontinue taking this class of antidepressant medication. This notion is further bolstered by the observation that the subjective evaluation of TCA medications was large and significant (i.e., 1.79, p = .01). PD patients would have not provided a positive evaluation of their TCA medication if they found them intolerable. Therefore, it can be concluded from this meta-analysis that TCAs provide physical and psychological health benefits to PD patients without the risk of substantial side effects.

In terms of MAOIs, the majority of side effects produced by selegeline were negative (see Table 14), but there were no significant effect sizes found within the distribution. Interestingly, more patients assigned to placebo evidenced depression relative to PD patients assigned to selegiline (i.e., $d = .15$, $p = .06$). Therefore, it is possible that selegeline may be able serve as a buffering agent for the development of depression in PD. Additionally, the results from this meta-analysis concur with the findings of Ives et al. (2004), in that our study did not find a significant effect size result on motor complications or mortality in patients that ranged from early to late PD. All things considered, selegeline does provide salutary health benefits to non-depressed PD patients without the risk of substantial side effects.

Limitations

It is acknowledged that the data from the present meta-analysis is limited by the inclusion of studies with low methodological quality even though randomized controlled trials were examined. One major problem with this literature is that there are no validated measurements for depression in PD (Leentjens et al., 2000). Therefore, the results from

this meta-analysis may have been drawn from studies that produced errors in measurement. Accordingly, measurement error can threaten the internal validity of meta-analytic findings. Therefore, the positive and significant effects observed with antidepressants on PD related depression should be viewed with caution.

Another limitation is the clinical homogeneity of patients found within the randomized controlled trials that were include into this meta-analysis. In general, patients in the clinical care setting are heterogeneous on many important characteristics that are normally controlled for by randomized controlled trials. For instance, clinical-care samples have various medical conditions and are usually receiving some other treatment outside the primary intervention. Furthermore, clinical-care samples are heterogeneous on factors such as age, culture, and gender. As a result, the treatment effectiveness observed with antidepressants from this meta-analysis may not generalize to PD patients that derive from the clinical care setting.

Future Directions

Future studies might benefit from looking at the impact of treating PD related depression on their caregivers and family members. It has been suggested that caregivers are at greater risk for developing health complications with the emergence of dementia, psychosis, and depression in PD (Ellgring, 1999). Therefore, it would be interesting to examine whether the salutary health benefits that were experienced by PD patients from this meta-analysis would also extend to caregivers and family members. This research may show that caregivers would develop a greater sense of self-efficacy, autonomy, and better economic outcomes as their partner's health is ameliorated with antidepressant

therapy. These three elements may reduce stress on caregivers and prevent physical and/or psychological morbidity.

Future studies should also examine the impact of "psychosocial interventions" among depressed PD patients and their caregivers. Evidence shows those PD patients who receive greater social support and engage in cognitive coping strategies are less likely to become depressed. For instance, Brown and McCarthy (1989) were one of the first to examine the influence of psychosocial variables in predicting depression for PD patients. Overall, the researchers found that the best predictors of depression were functional disability, self-esteem, and avoidant coping. Together, these variables accounted for 46% of the variance in depression. Furthermore, the researchers observed that positive affect and cognitive coping (e.g., acceptance of illness) were significantly correlated with lower depression.

Additional evidence on the moderating role of coping style and social support on depression in PD was observed in a study conducted by Dakoff and Mendelson (1989). In their research, they were able to identify three types of coping strategies used by PD patients and how they were related to poorer mental health. Overall, the research showed that those individuals that were in sound psychological health utilized more cognitive coping strategies to deal with their PD (e.g., believes mental attitude can effect PD and that there are worse fates than PD). However, the researchers also found that those patients who were mildly depressed engaged in less cognitive coping, but still engaged and enjoyed social interactions. Finally, for those individuals that were severely depressed, they did not engage in cognitive coping and were socially isolated relative to the other groups. Together, these results show that cognitive coping and social

support/functioning can buffer the PD patient against the effects of their stressful disease even in the face of moderate to severe disability.

Frazier (2000) also lends support to the notion that psychosocial factors can influence depression in PD. The researcher examined the influence of coping strategies (i.e., active coping, emotion regulation, and avoidant coping) in addition to disease-related variables (i.e., PD severity, duration of illness, and effectiveness of medication) on health-related quality of life in PD patients. Overall, the researcher found that disease-related variables and the use of avoidant coping strategies were the best predictors of perceived distress. Furthermore, it was found that the use of avoidant coping strategies was the best predictor of poorer emotional well-being (i.e., depression) in PD patients, but disease related variables such functional disability did contribute to some of the variance in emotional well-being (Frazier, 2000). Finally, both disease related variables and the use of avoidant coping predicted poorer social functioning (Frazier, 2000). Once again, the results of this study show the type of coping style used by the PD patient has a strong influence on their mental health outcomes and social functioning.

Perhaps the best evidence to show that psychosocial factors (e.g., coping strategies) plays an important role in the health outcomes of PD patients derives from a recent longitudinal study. Frazier (2002) observed that PD patients who modified their coping strategies from active (i.e., behavioral) to emotion regulation (i.e., venting emotions, cognitive reinterpretation, introspection) over the course of two years evidenced less psychological distress and greater quality of life at study outset relative to those individuals that continued to use active or avoidant coping. It was concluded by the author that if PD patients are trained to cognitively reframe and express emotions toward

the physical and psychological distress that is associated with PD, these patients will acquire a sense of mastery over their disorder and experience better physical and psychological health (Frazier, 2002).

Taken together, the effects of a psychosocial intervention should be systematically explored as a treatment option for depression in PD. Psychoeducation, family counseling, and cognitive-behavioral therapy may improve the health-related quality of life of PD patients by encouraging emotional expression (i.e., the communication of stress) while teaching adaptive coping strategies among patients and their partners (Ellgring, 1999). However, for those PD patients seeking relief for their affective disturbances through pharmacotherapy, this meta-analysis showed that TCAs have the most tangible effects on depression. However, the decision to use TCAs should be weighted against their potential risk of side effects.

Conclusions

There has been confusion about the safety and efficacy of antidepressant use in PD. As a result, many depressed PD patients have been left untreated to cope with their affective disturbances (Huber et al., 1988; Mayeux et al., 1986; Starkstein et al., 1990). However, the results from this meta-analysis can guide physicians in determining which treatment options are best for their depressed PD patient. Therefore, the present study has important clinical implications by potentially increasing the number of patients that can safely be treated with antidepressants.

It was observed from this study that TCAs had a robust treatment effect on depression in general, and particularly for those PD patients suffering with severe depression. However, it was also observed that TCAs produced a mild side-effect profile.

On the other hand, SSRIs did not exacerbate PD motor symptoms or produce any other significant adverse events. However, SSRIs were only effective on PD patients with less severe (i.e., mild-moderate) forms of depression. Accordingly, the present meta-analysis recommends that antidepressants should be prescribed according to the same principles that are followed as in elderly patients without PD. More specifically, the choice of antidepressant must be based on a favorable profile of side-effects, depression severity, and the general health status of the PD patient. Nonetheless, before PD patients can be treated, they need to be diagnosed with depression. Although there are no validated measures of depression in PD (Leentjens et al., 2000), it is recommended that physicians actively look for several depressive symptoms that have been commonly associated with PD (Cote, 1999).

Cote (1999) observed that PD patients that have depression as a major affective disorder often admit to feelings of hopelessness, worthlessness, loss of interest in pleasurable activities, and changes in appetite. Interestingly, it has also been observed that PD patients that are not depressed have excellent appetites whereas depressed PD patients usually exhibit severe weight loss. Therefore, physicians may be able to discriminate between the primary motor pathology of PD and depression by simply looking at dietary preferences (Cote, 1999). In short, programs of research which focus on the measurement of depression in PD are urgently needed.

Table 1
Effect size, Correlations, Significance, Antidepressant drug and Class, Outcome Types, and Clinical Populations for Each Study

Study	Number ES per Study	*N*	*d*	*r*	Drug *& Class*	Outcome *Type*	Clinical *Population*
Anderson, Aabro, Gulmann, Helmsted, & Pedersen (1980)	11	19	.32	.15	Nortriptyline/ TCA	*AB*	Depressive Symptoms[2]
Indaco & Carrieri (1988)	11	31	.99	.37	Amitriptyline/ TCA	*AB*	Depressive Symptoms[2]
Laitinen (1969)	11	39	.11	.04	Desipramine/ TCA	*AB*	Depressed[2]
Strang (1965)	6	28	.52	.25	Imipramine/ TCA	AB	Depressed[2]
Chung & Nutt (2004)	3	14	.13	.06	Paroxetine/ SSRI	A	Non-Depressed[2]
Fregni, Santos, Myczkowski, Rigolino, Gallucci-Neto, & Barbosa et al. (2004)	4	21	.95	.34	Paroxetine/ SSRI	AB	Depressed[2]
Leentjens, Vreeling, Luijckx & Verhey (2003)	2	12	.43	.24	Citalopram/ SSRI	AB	Depressed[3]
Rampello, Chiechio, Raffaele, Vecchio, & Nicoletti (2002)	10	31	1.00	.44	Citalopram/ SSRI	A	Non-Depressed & Depressed[2]

Table 1
Effect size, Correlations, Significance, Antidepressant drug and Class, Outcome Types, and Clinical Populations for Each Study

Study	Number ES per Study	*N*	*d*	*r*	Drug & *Class*	Outcome *Type*	Clinical *Population*
Wermuth, Sorensen, Timm, Christensen, Utzon, & Boas et al. (1998)	23	23	.17	.08	Citalopram/ SSRI	AB	Depressed[2]
Allain, Cougnard, Neukirch, & The FSMT members (1991)	17	82	.09	.04	Selegiline/ MAOI	AB	Depressive Symptoms[1]
Allain, Pollak, & Neukirch (1993)	19	82	.14	.07	Selegiline/ MAOI	AB	Depressive Symptoms[1]
Caracenni & Musicco (2001)	8	303	.02	.00	Selegiline/ MAOI	A	Non-Depressed[1]
Dalrymple-Alford, Jamieson, & Donaldson (1995)	15	20	.09	.04	Selegiline/ MAOI	AB	Depressed[1]
Dixit, Behari, & Ahuja (1999)	5	32	1.07	.46	Selegiline/ MAOI	AB	Non-Depressed[2]
Frankel, Kempster, Stibe, Eatough, Nathanson, & Lees et al. (1989)	4	24	.13	.07	Selegiline/ MAOI	A	Non-depressed[2]
Golbe & Duvoisin (1987)	16	32	-.16	-.08	Selegiline/ MAOI	AB	Non-Depressed[3]
Hietanen (1991)	18	36	-.11	-.06	Selegiline/ MAOI	AB	Depressive Symptoms[2]
Hubble, Koller, & Waters (1993)	11	32	-.06	-.03	Selegiline/ MAOI	A	Non-Depressed[2]

Table 1
Effect Size, Correlations, Significance, Antidepressant drug and Class, Outcome Types, and Clinical Populations for Each Study

Study	Number ES per Study	*N*	*d*	*r*	Drug & Class	Outcome Type	Clinical Population
Kieburtz, McDermott, Como, Growdon, Brady, & Carter et al. (1994)	11	361	-.00	-.00	Selegiline/ MAOI	A	Non-Depressed[1]
Kirollos, Charlett, Bowes, Purkiss, O'Neill, & Weller et al. (1996)	18	25	.20	.09	Selegiline/ MAOI	AB	Non-Depressed[1]
Larson, Boas, & Erdal (1999)	20	138	.06	.03	Selegiline/ MAOI	AB	Non-Depressed[1]
Lees, Kohout, Shaw, Stern, Elsworth, & Sandler et al. (1977)	13	38	-.38	-.17	Selegiline/ MAOI	AB	Depressed[3]
Lieberman, Gopinathan, Neophytides, & Foo (1987)	6	33	.37	.16	Selegiline/ MAOI	A	Non-Depressed[2]
Mally, Kovacs, & Stone (1995)	30	20	.63	.30	Selegiline/ MAOI	A	Non-Depressed[1]
Myllyla, Sotaniemi, Vuorinen, & Heinonen (1991)	5	52	.40	.19	Selegiline/ MAOI	A	Non-Depressed[1]
Myllyla, Sotaniemi, Vuorinen, & Heinonen (1992)	20	52	.24	.12	Selegiline/ MAOI	A	Non-Depressed[1]

Table 1 Continued
Effect size, Correlations, Significance, Antidepressant drug and Class, Outcome Types, and Clinical Populations for Each Study

Study	Number ES per Study	*N*	*d*	*r*	Drug & *Class*	Outcome *Type*	Clinical *Population*
Myllyla, Sotaniemi, Vuorinen, & Heinonen (1993)	17	44	.28	.13	Selegiline/ MAOI	A	Non-Depressed[1]
Myllyla, Heinonen, Vuorinen, Kikku, & Sotaniemi (1995)	52	44	.16	.07	Selegiline/ MAOI	A	Non-Depressed[1]
Myllyla, Sotaniemi, Hakulinen, Maki-Ikola, & Heinonen (1997)	22	48	.22	.11	Selegiline/ MAOI	A	Non-Depressed[1]
Nappi, Martignoni, Horowski, Pacchetti, Rainer, & Bruggi et al. (1991)	15	20	.57	.27	Selegiline/ MAOI	A	Non-Depressed[1]
Olanow, Hauser, Gauger, Malapira, Koller, & Hubble et al. (1995)	6	43	.13	.07	Selegiline/ MAOI	A	Non-Depressed[1]
Palhagen, Heinonen, Hagglund, Kaugesaar, Kontants, & Maki et al. (1998)	21	85	.36	.13	Selegiline/ MAOI	A	Non-Depressed[1]

Table 1 Continued
Effect size, Correlations, Significance, Antidepressant drug and Class, Outcome Types, and Clinical Populations for Each Study

Study	Number ES per Study	*N*	*d*	*r*	Drug & *Class*	Outcome *Type*	Clinical *Population*
Parkinson Study Group (1989)	28	765	.17	.08	Selegiline/ MAOI	A	Non-Depressed[1]
Parkinson Study Group (1993)	15	401	.19	.09	Selegiline/ MAOI	A	Non-Depressed[1]
Parkinson Study Group (1998)	1	800	-.02	-.01	Selegiline/ MAOI	A	Non-Depressed[1]
Przuntek & Kuhn (1987)	12	58	-.05	-.03	Selegiline/ MAOI	AB	Depressive Symptoms[1]
Przuntek, Conrad, Dichgans, Kraus, Krauseneck, & Pergande et al. (1999)	14	78	.52	.24	Selegiline/ MAOI	A	Non-Depressed[1]
Schoulson, Oaks, Fahn, Lang, Langston, & LeWitt et al. (2002)	26	354	.09	.04	Selegiline/ MAOI	AB	Non-Depressed[2]
Shults & The Parkinson Study Group (1993)	15	777	.16	.08	Selegiline/ MAOI	AB	Depressive Symptoms[2]
Siversten, Dupont, Mikkelsen, Mogensen, Rasmussen, & Boesen et al. (1989)	7	30	-.09	-.04	Selegiline/ MAOI	A	Non-Depressed[2]

Table 1 Continued
Effect size, Correlations, Significance, Antidepressant drug and Class, Outcome Types, and Clinical Populations for Each Study

Study	Number ES per Study	*N*	*d*	*r*	Drug *& Class*	Outcome *Type*	Clinical *Population*
Takahashi, Yuasa, Imai, Tachibana, Yorifuji,& Nakamura et al. (1994)	22	99	.20	.09	Selegiline/ MAOI	A	Non-Depressed[2]
Tetrud & Langston (1989)	16	52	.30	.14	Selegiline/ MAOI	A	Non-Depressed[1]
Teychenne & Parker (1989)	8	10	.90	.37	Selegiline/ MAOI	A	Non-Depressed[2]
Turkka, Suominen, Tolonen, Sotaniemi, & Myllyla (1997)	3	97	-.42	-.21	Selegiline/ MAOI	A	Non-Depressed[2]
Waters, Sethi, Hauser, Molho, Bertoni, & The Zydis Selegiline Study Group (2004)	15	140	.19	.09	Selegiline/ MAOI	A	Non-Depressed[2]
Overall Mean Weighted Effect Size Results	*632*	*5539*	*.13*	*.06*	*p = .00*		*95% CI = .07 /.18*

Note. Outcome types are indicated as A=Physical health, B=Psychological health; Disease severity indicated as 1=Early PD, 2=Middle PD, 3= Late PD

Table 2
Summary of Effect Sizes for Each Health Outcome

Specific Outcomes	N	Number of ES per Outcome	*k*	Fail-safe *k*	*d*	*r*	*p*	95% CI	*Q* (HT)
Neurological-motor	4132	277	36	86	.26	.15	.00	.20 / .32	41.71
Cardiac	63	7	2	14	.30	.16	.11	-.19 / .80	.12
Pain-discomfort	186	6	1	74	1.78	.67	.00	1.33 / 2.00	6.19
Health Related Quality of Life	2803	51	9	18	.23	.11	.00	.16 / .30	14.15
Depression	2581	33	18	25	.25	.12	.02	.02 / .49	38.71**
Depression (Trimmed)	2485	30	16	15	.11	.05	.00	.03 / .19	16.14
Subjective evaluation of medications	65	3	2	20	.88	.39	.00	.37 / 1.39	.24
Global psychological function	2661	33	12	28	.22	.11	.00	.14 / .30	7.66
Cognition	553	49	6	0	.09	.04	.15	-.08 / .25	10.12
Overall	*13044*	*459*		*28*	*.28*	*.13*	*.00*	*.14 / .38*	*15.79**
Overall (Trimmed)	*12948*	*456*		*26*	*.25*	*.12*	*.00*	*.12 / .39*	*16.77**

Note. *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * $p < .05$. ** $p < .01$. Trimmed effect size results were calculated because of the presence of outliers found in the SSRI depression sub-analyses.

Table 3

Summary of Effect Sizes for Each Side Effect

Specific Outcomes	N	Number of ES per Side Effect	*k*	Fail-safe *k*	*d*	r	*p*	95% CI	*Q* (HT)
Neurological-motor	1714	16	36	11	-.16	-.06	.14	-.40 / .08	37.97
Autonomic	2572	39	15	20	-.14	-.07	.00	-.22 / -.06	19.53
Pain-discomfort	798	13	12	13	-.20	-.10	.01	-.34 / -.06	5.17
Depression	658	5	5	2	.15	.07	.06	.00 / .30	.56
Global psychological function	1212	30	16	0	-.03	-.03	.50	-.15 / .08	23.82
Cognition	532	7	6	13	-.13	-.05	.05	-.31 / .04	6.49
Gastrointestinal	2371	42	20	0	-.06	-.03	.07	-.18 / .05	26.90
Urological	71	2	2	8	-.32	-.24	.09	-.78 / .15	.00
Mortality	2125	8	8	0	-.06	-.03	.10	-.14 / .03	8.58
Overall	*12053*	*162*		*2*	*-.08*	*-.04*	*.09*	*-.20 / .04*	*2.92*

Note. *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * p < .05. ** p < .01.

Table 4
Summary of Effect Sizes for Physical Health Outcome

Specific Outcomes	N	Number of ES per Outcome	*k*	Fail-safe *k*	*d*	*r*	*p*	*Q* (HT)
Neurological-motor	4132	277	36	86	.26	.15	.00	41.71
Cardiac	63	7	2	14	.30	.16	.12	.12
Pain-discomfort	186	6	1	74	1.78	.67	.00	6.19
Health Related Quality of Life	2803	51	9	18	.23	.11	.00	14.15
Overall	*7184*	*341*		*18*	*.45*	*.15*	*.03*	*11.86**

Note. *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * $p < .05$. ** $p < .01$.

Table 5
Summary of Effect Sizes for Psychological Health Outcomes

Specific Outcomes	N	Number of ES per Outcome	*k*	Fail-safe *k*	*d*	*r*	*p*	*Q* (HT)
Depression	2581	33	18	25	.25	.12	.02	38.71**
Depression (trimmed)	2485	30	16	15	.11	.05	.00	16.14
Subjective evaluation of medications	65	3	2	20	.88	.39	.00	.24
Global psychological function	2661	33	12	18	.22	.11	.00	7.66
Cognition	553	49	6	0	.09	.04	.16	10.12
Overall	5860	118		*9*	*.26*	*.11*	*.02*	*3.52*
Overall (Trimmed)	5764	115		*8*	*.22*	.08	*.05*	*3.93*

Note . *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * p < .05. ** p < .01. Trimmed effect size results were calculated because of the presence of outliers found in the SSRI depression sub-analyses.

Table 6
Effect sizes, Correlations, Significance, Outcome Type, Clinical Population for Each TCA Study

Study	*N*	*d*	*r*	Drug & *Class*	Outcome *Type*	Clinical *Population*
Anderson, Aabro, Gulmann, Helmsted, & Pedersen (1980)	19	.30	.14	Nortriptyline/ TCA	*AB*	Depressive Symptoms[2]
Indaco & Carrieri (1988)	31	1.03	.38	Amitriptyline/ TCA	*AB*	Depressive Symptoms[2]
Laitinen (1969)	39	.11	.04	Desipramine/ TCA	*AB*	Depressed[2]
Strang (1965)	28	.53	.25	Imipramine/ TCA	AB	Depressed[2]
Overall Mean Weighted Effect Size	117	.42	.20	*p* = .01	*Qw* =	3.23, p = . 36

Note. Outcome types are indicated as A=Physical health, B=Psychological health

Table 7
Effect sizes, Correlations, Significance, Outcome Type, and Clinical Population for Each SSRI Study

Study	*N*	*d*	*r*	Drug & *Class*	Outcome *Type*	Clinical *Population*
Chung & Nutt (2004)	14	.13	.06	Paroxetine/ SSRI	A	Non-Depressed[2]
Fregni, Santos, Myczkowski, Rigolino, Gallucci-Neto, & Barbosa et al. (2004)	21	.94	.34	Paroxetine/ SSRI	AB	Depressed[2]
Leentjens, Vreeling, Luijckx & Verhey (2003)	12	.54	.24	Citalopram/ SSRI	AB	Depressed[3]
Rampello, Chiechio, Raffaele, Vecchio, & Nicoletti (2002)	31	1.02	.44	Citalopram/ SSRI	A	Non-Depressed & Depressed[2]
Wermuth, Sorensen, Timm, Christensen, Utzon, & Boas et al. (1998)	23	.18	.08	Citalopram/ SSRI	AB	Depressed[2]
Overall Mean Weighted Effect Size	101	.53	.26	p =.003		*Qw* = 4.07, p = .40

Note. Outcome types are indicated as A=Physical health, B=Psychological health

Table 8
Effect sizes, Correlations, Significance, Outcome Type, and Clinical Populations for Each MAOI Study

Study	*N*	*d*	*r*	Drug & *Class*	Outcome *Type*	Clinical *Population*
Allain, Cougnard, Neukirch, & The FSMT members (1991)	82	.09	.04	Selegiline/ MAOI	AB	Depressive Symptoms[1]
Allain, Pollak, & Neukirch (1993)	82	.14	.07	Selegiline/ MAOI	AB	Depressive Symptoms[1]
Caracenni & Musicco (2001)	303	.02	.00	Selegiline/ MAOI	A	Non-Depressed[1]
Dalrymple-Alford, Jamieson, & Donaldson (1995)	20	.09	.04	Selegiline/ MAOI	AB	Depressed[1]
Dixit, Behari, & Ahuja (1999)	32	1.07	.46	Selegiline/ MAOI	AB	Non-Depressed[2]
Frankel, Kempster, Stibe, Eatough, Nathanson, & Lees et al. (1989)	24	.13	.07	Selegiline/ MAOI	A	Non-depressed[2]
Golbe & Duvoisin (1987)	32	-.16	-.08	Selegiline/ MAOI	AB	Non-Depressed[3]
Hietanen (1991)	36	-.11	-.06	Selegiline/ MAOI	AB	Depressive Symptoms[2]
Hubble, Koller, & Waters (1993)	32	-.06	-.03	Selegiline/ MAOI	A	Non-Depressed[2]
Kieburtz, McDermott, Como, Growdon, Brady, & Carter et al. (1994)	361	-.00	-.00	Selegiline/ MAOI	A	Non-Depressed[1]

Table 8 continued
Effect sizes, Correlations, Significance, Outcome Type, and Clinical Populations for Each MAOI Study

Study	*N*	*d*	*r*	Drug *& Class*	Outcome *Type*	Clinical *Population*
Kirollos, Charlett, Bowes, Purkiss, O'Neill, & Weller et al. (1996)	25	.20	.09	Selegiline/ MAOI	AB	Non-Depressed[1]
Larson, Boas, & Erdal (1999)	138	.06	.03	Selegiline/ MAOI	AB	Non-Depressed[1]
Lees, Kohout, Shaw, Stern, Elsworth, & Sandler et al. (1977)	38	-.38	-.17	Selegiline/ MAOI	AB	Depressed[3]
Lieberman, Gopinathan, Neophytides, & Foo (1987)	33	.37	.16	Selegiline/ MAOI	A	Non-Depressed[2]
Mally, Kovacs, & Stone (1995)	20	.63	.30	Selegiline/ MAOI	A	Non-Depressed[1]
Myllyla, Sotaniemi, Vuorinen, & Heinonen (1991)	52	.40	.19	Selegiline/ MAOI	A	Non-Depressed[1]
Myllyla, Sotaniemi, Vuorinen, & Heinonen (1992)	52	.24	.12	Selegiline/ MAOI	A	Non-Depressed[1]
Myllyla, Sotaniemi, Vuorinen, & Heinonen (1993)	44	.28	.13	Selegiline/ MAOI	A	Non-Depressed[1]

Table 8 continued
Effect sizes, Correlations, Significance, Outcome Type, and Clinical Populations for Each MAOI Study

Study	*N*	*d*	*r*	Drug *& Class*	Outcome *Type*	Clinical *Population*
Myllyla, Heinonen, Vuorinen, Kikku, & Sotaniemi (1995)	44	.16	.07	Selegiline/ MAOI	A	Non-Depressed[1]
Myllyla, Sotaniemi, Hakulinen, Maki-Ikola, & Heinonen (1997)	48	.22	.11	Selegiline/ MAOI	A	Non-Depressed[1]
Nappi, Martignoni, Horowski, Pacchetti, Rainer, & Bruggi et al. (1991)	20	.57	.27	Selegiline/ MAOI	A	Non-Depressed[1]
Olanow, Hauser, Gauger, Malapira, Koller, & Hubble et al. (1995)	43	.13	.07	Selegiline/ MAOI	A	Non-Depressed[1]
Palhagen, Heinonen, Hagglund, Kaugesaar, Kontants, & Maki et al. (1998)	85	.36	.13	Selegiline/ MAOI	A	Non-Depressed[1]
Parkinson Study Group (1989)	765	.17	.08	Selegiline/ MAOI	A	Non-Depressed[1]

Table 8 continued
Effect sizes, Correlations, Significance, Outcome Type, and Clinical Populations for Each MAOI Study

Study	*N*	*d*	*r*	Drug & *Class*	Outcome *Type*	Clinical *Population*
Parkinson Study Group (1993)	401	.19	.09	Selegiline/ MAOI	A	Non-Depressed[1]
Parkinson Study Group (1998)	800	-.02	-.01	Selegiline/ MAOI	A	Non-Depressed[1]
Przuntek & Kuhn (1987)	58	-.05	-.03	Selegiline/ MAOI	AB	Depressive Symptoms[1]
Przuntek, Conrad, Dichgans, Kraus, Krauseneck, & Pergande et al. (1999)	78	.52	.24	Selegiline/ MAOI	A	Non-Depressed[1]
Schoulson, Oaks, Fahn, Lang, Langston, & LeWitt et al. (2002)	354	.09	.04	Selegiline/ MAOI	AB	Non-Depressed[2]
Shults & The Parkinson Study Group (1993)	777	.16	.08	Selegiline/ MAOI	AB	Depressive Symptoms[2]
Siversten, Dupont, Mikkelsen, Mogensen, Rasmussen, & Boesen et al. (1989)	30	-.09	-.04	Selegiline/ MAOI	A	Non-Depressed[2]
Takahashi, Yuasa, Imai, Tachibana, Yorifuji,& Nakamura et al. (1994)	99	.20	.09	Selegiline/ MAOI	A	Non-Depressed[2]

Table 8 continued
Effect sizes, Correlations, Significance, Outcome Type, and Clinical Populations for Each MAOI Study

Study	*N*	*d*	*r*	Drug & *Class*	Outcome *Type*	Clinical *Population*
Tetrud & Langston (1989)	52	.30	.14	Selegiline/ MAOI	A	Non-Depressed[1]
Teychenne & Parker (1989)	10	.90	.37	Selegiline/ MAOI	A	Non-Depressed[2]
Turkka, Suominen, Tolonen, Sotaniemi, & Myllyla (1997)	97	-.42	-.21	Selegiline/ MAOI	A	Non-Depressed[2]
Waters, Sethi, Hauser, Molho, Bertoni, & The Zydis Selegiline Study Group (2004)	140	.19	.09	Selegiline/ MAOI	A	Non-Depressed[2]
Overall Mean Weighted Effect Size Results		.11	.05	$p = .00$		Qw= 36.44, $p = .40$

Table 9
Summary of Effect Sizes for Each Health Outcome for TCA Studies

Specific Outcomes	N	Number of ES per Outcome	*k*	Fail-safe *k*	*d*	*r*	*p*	95% CI	*Q* (HT)
Neurological-motor	84	12	3	25	.30	.15	.07	-.09 / .70	.16
Cardiac	19	3	1	4	.23	.12	.11	-.13 / .60	.04
Pain-discomfort	31	6	1	74	1.79	.67	.00	1.33 / 2.00	6.19
Health Related Quality of Life	0	0	0	___	____	____	___	_____	____
Depression	117	4	4	18	.55	.24	.01	.19 / .90	5.98
Subjective evaluation of medications	31	1	1	N/A	1.02	.46	.01	.37 / 1.39	.24
Global psychological function	77	3	2	21	.81	.40	.00	.30 / 1.32	.68
Cognition	0	0	0	___	____	____	___	_____	____
Overall	*359*	*29*		*35*	*.68*	*.30*	*.00*	*.40 / .97*	*10.35*

Note. (-) = no study assessed outcome and not averaged into *d*. *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * $p < .05$. ** $p < .01$.

Table 10
Summary of Effect Sizes for Side Effects in Each TCA Study

Specific Outcomes	N	Number of ES per Side Effect	*k*	Fail-safe *k*	*d*	*r*	*p*	95% CI	*Q* (HT)
Neurological-motor	0	0	0	____	____	___	____	_____	____
Cardiac	39	1	1	N/A	-.31	-.16	.34	-.33 / .93	NA
Pain-discomfort	31	1	1	N/A	-.37	-.19	.31	-.35 / 1.07	NA
Depression	0	0	0	____	____	___	____	_____	____
Global psychological function	70	2	2	8	-.47	-.24	.03	.06 / .24	.58
Cognition	39	1	1	N/A	-.31	-.16	.34	-.33 / .93	NA
Gastrointestinal	70	4	2	4	.10	.01	.35	-.37 / .57	.82
Urological	39	1	1	N/A	-.31	-.16	.34	-.33 / .93	NA
Mortality	0	0	0	____	____	___	____	_____	____
Overall	*288*	*10*		*12*	*-.27*	*-.14*	*.02*	*-.53 / -.01*	*1.64*

Note. Note. (-) = no study assessed outcome and not averaged into *d*. *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * $p < .05$. ** $p < .01$.

Table 11
Summary of Effect Sizes for Each Health Outcome for SSRIs Studies

Specific Outcomes	N	Number of ES per Outcome	*k*	Fail-safe *k*	*d*	*r*	*p*	95% CI	*Q* (HT)
Neurological-motor	100	14	4	32	.34	.27	.04	-.04 / .72	6.29
Cardiac	0	0	0	___	___	___	___	_____	_____
Pain-discomfort	0	0	0	___	___	___	___	_____	_____
Health Related Quality of Life	22	4	1	11	.32	.17	.07	-.10 / .75	.18
Depression	286	11	4	39	.58	.21	.00	.33 / .82	36.54**
Depression (Trimmed)	192	9	3	12	.21	.11	.08	-.07 / .48	4.65
Subjective evaluation of medications	0	0	0	___	___	___	___	_____	_____
Global psychological function	20	6	1	9	.24	.13	.10	-.13 / .60	.58
Cognition	0	0	0	__	___	___	___	_____	____
Overall	*428*	*35*		*16*	*.36*	*.22*	*.00*	*.00 / .76*	*.36*
Overall (Trimmed)	*334*	*33*		10	*.25*	.16	*.00*	*-.09 / .42*	*.43*

Note. (-) = no study assessed outcome and not averaged into *d*. *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * p < .05. ** p < .01.

Table 12
Summary of Effect Sizes for Side Effects in Each SSRIs Study

Specific Outcomes	N	Number of ES per Side Effect	*k*	Fail-safe *k*	*d*	*r*	*p*	95% CI	*Q* (HT)
Neurological-motor	0	0	0	___	____	___	____	_____	___
Cardiac	0	0	0	___	____	___	____	_____	___
Pain-discomfort	0	0	0	___	____	___	____	_____	___
Depression	0	0	0	___	____	___	____	_____	___
Global psychological function	30	3	1	5	.27	.14	.11	-.16 / .69	3.73
Cognition	0	0	0	___	____	___	____	_____	___
Gastrointestinal	30	2	1	4	-.27	-.15	.15	-.79 / .24	.31
Urological	0	0	0	___	____	___	____	_____	___
Mortality	0	0	0	___	____	___	____	_____	___
Overall	*60*	*5*	*1*	*2*	*-.002*	*-.01*	*.50*	*-.51 / .51*	*1.00*

Note. (-) = no study assessed outcome and not averaged into *d*. *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * $p < .05$. ** $p < .01$.

Table 13
Summary of Effect Sizes for Each Health Outcome for MAOIs Studies

Specific Outcomes	N	Number of ES per Outcome	*k*	Fail-safe *k*	*d*	*r*	*p*	95% CI	*Q* (HT)
Neurological-motor	3948	251	28	26	.36	.15	.00	.09 / .36	13.65
Cardiac	25	3	1	17	.41	.33	.04	-.05 / .87	.30
Pain-discomfort	0	0	0	__	____	__	____	____	____
Health Related Quality of Life	2781	43	13	32	.23	.11	.00	.15 / .30	14.08
Depression	2336	17	10	0	.08	.04	.03	.00 / .16	2.16
Subjective evaluation of medications	68	2	1	12	.73	.35	.00	.23 / 1.22	1.22
Global psychological function	2564	24	9	15	.21	.10	.00	.13 / .29	1.68
Cognition	532	49	6	11	.09	.04	.16	-.08 / .25	10.12
Overall	*9172*	*258*		*15*	*.20*	*.09*	*.00*	*.07 / .32*	*3.25*

Note. (-) = no study assessed outcome and not averaged into *d*. *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * $p < .05$. ** $p < .01$.

Table 14
Summary of Effect Sizes for Side Effects in Each MAOIs Study

Specific Outcomes	N	Number of ES per Side Effect	*k*	Fail-safe k	*d*	*r*	*p*	95% CI	*Q* (HT)
Neurological-motor	1762	16	11	11	-.16	-.05	.14	-.40 / .08	37. 97
Cardiac	2503	37	15	12	-.13	-.07	.00	-.21 / -.05	17.19
Pain-discomfort	737	11	10	11	-.20	-.11	.00	.01 / .07	3.83
Depression	658	5	5	2	.15	.07	.06	.00 / .30	.56
Global psychological function	1164	25	13	2	-.04	-.02	.25	-.15 / .08	22.78*
Cognition	493	6	4	12	-.12	-.06	.09	-.30 / .06	6.18
Gastrointestinal	2233	36	17	5	-.06	-.04	.15	-.15 / .02	24.79
Urological	32	1	1	N/A	-.33	-.17	.36	-.78 / .15	N/A
Mortality	2125	8	8	7	-.06	-.03	.10	-.14 / .03	8.58
Overall	*11707*	*145*		*1*	*-.07*	*-.04*	*.11*	*-.19 / .04*	*2.87*

Note. (-) = no study assessed outcome and not averaged into *d*. *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * $p < .05$. ** $p < .01$.

Table 15
Stem-and-Leaf Display of the Mean Weighted Effect size for Antidepressants on Depression Outcomes.

Stem	Leaf
2.0	0
1.0	2, 3, 9
.9	
.8	
.7	2
.6	
.5	1, 1, 6
.4	
.3	1, 5, 9,
.2	
.1	3, 4, 4
.0	0, 0, 0, 0, 0, 0, 3, 4, 6
-.0	1, 4, 5, 5, 7, 7
-.1	
-.2	2, 4, 7

Table 16
Stem-and-Leaf Display of the Effect Sizes for SSRI Antidepressants on Depression Outcomes.

Stem	Leaf
2.0	2
1.	3, 9
.9	
.8	
.7	
.6	
.5	
.4	
.3	1
.2	
.1	
.0	3
-.0	1, 3, 5
-.1	
-.2	2

Table 17
A 2x2 Binomial Effect Size Distribution for SSRIs on Depression

Clinical Population	Percentage of Success	Percentage of Failure
Antidepressant Groups	56%	44%
Placebo Control Groups	44%	56%

Table 18
A 2x2 Binomial Effect Size Distribution for MAOIs on Depression

Clinical Population	Percentage of Success	Percentage of Failure
Antidepressant Groups	52%	48%
Placebo Control Groups	48%	52%

Table19
Depression Severity

Specific Outcomes	N	Number of ES per Outcome	*k*	Number of Studies Contributing to Each Drug Class TCA	SSRI	MAOI	*d*	*p*	95% CI	*Q* (HT)
Depressive Symptoms	2272	15	8	0	0	8	.08	.02	.00 / .17	1.40
Mild Depression	156	5	5	4	0	1	.43	.00	.11 / .76	8.54
Moderate Depression	198	5	3	0	2	1	.27	.01	-.10 / .64	1.50
Major Depression	132	7	2	0	2	0	.01	.47	-.34 / .37	.52

Note. *k*= number of studies per outcome. CI = confidence interval. Q(HT) = homogeneity test. * $p < .05$. ** $p < .01$.

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Note. * indicates studies to be included in this meta-analysis.