# Exploring the Impact of SSRI-induced Apathy on Depression Treatment Outcomes in Parkinson's Disease Patients

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## Abstract

Selective serotonin reuptake inhibitors (SSRIs) were found to be associated with increased apathy in Parkinson's disease patients compared to other classes of antidepressants (Kenney et. al, 2023). SSRIs may downregulate dopamine and contribute to neurodegeneration of dopaminergic neurons in Parkinson's disease (PD). While, this phenomenon of SSRI-induced apathy has not been analyzed through the perspective its impact on the quality of life and depression treatment outcomes of PD patients. Through a qualitative synthesis of existing literature on the topic, the question I seek to explore is: To what extent does SSRI-induced apathy significantly worsen depression treatment outcomes in Parkinson's disease patients? Using databases PUBMED and Proquest, I evaluated qualitative themes in papers related to either SSRI-induced apathy in PD, apathy and depression's distinction, and how apathy and depression affects the quality of life of PD patients. I discovered a recurring theme that SSRI-induced apathy is significant and can instigate a cyclical nature of the worsening of depression treatment outcomes, apathy symptoms, cognition, motor symptoms, and quality of life of PD patients in general. These findings highlight the need for clinicians to tailor treatment for depression in PD patients and distinguish diagnostic criteria for apathy and depression.

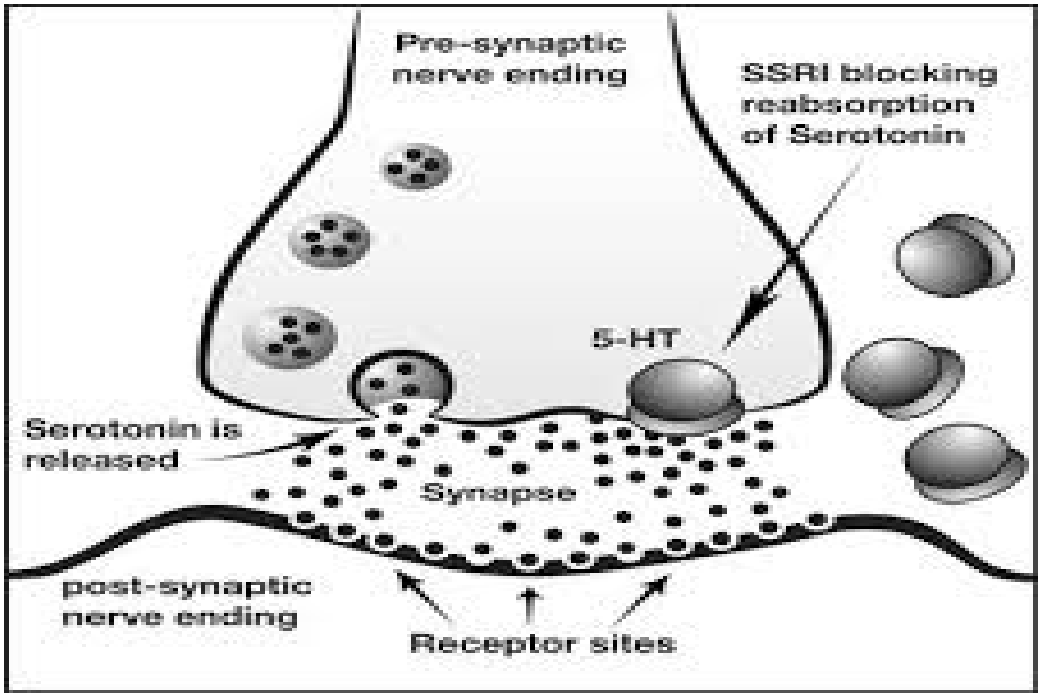

## Introduction

As defined by Maher et. al (2024), Parkinson's disease (PD) is characterized as a progressive neurodegenerative disorder caused by cell loss in the substantia nigra, which supplies dopaminergic innervation to the basal ganglia. Despite its classification as a neurodegenerative disorder, Aguera-ortiz and colleagues (2021) suggest that PD is classified as a

neuropsychiatric disease rather than movement disorder. Along with the motor symptoms associated with PD, the journal *Nature Mental Health* emphasizes that depression affects as much as a third of PD patients, is correlated with increased mortality, greater disability, and has a greater negative effect on health-related quality of life than motor symptoms (Costello et. al, 2024).

**Figure 1**

*SSRIs functioning to block serotonin reuptake*




To resolve the high prevalence of depression within PD patients, it is often vital for pharmacological treatment to alleviate severe depression symptoms, especially considering the other motor symptoms PD patients commonly experience. Padala et. al (2020) establish that selective serotonin reuptake inhibitors (SSRIs) are often considered to be first-line treatment for depression, preferred over other agents due to their relatively favorable safety profile and ease of

administration. Best et. al (2010) clarify that polymorphisms in the serotonin reuptake transporter (SERT) gene are associated with depression, and SSRIs function to downregulate SERTs, blocking reabsorption of serotonin and increasing serotonin levels in the brain.

Apathy is defined by Masdrakis et. al (2023) in *Acta Neuropsychiatrica* as a syndrome whose main clinical characteristic is a primary motivation loss due to any emotional distress, intellectual impairment, emotional distress, or decreased consciousness, etc. Kenney et. al (2023) measured depression and apathy and depression in a sample of 387 PD patients treated with SSRIs and SNRIs and discovered that individuals taking SSRIs or SNRIs were more likely to be clinically apathetic than those taking other depression medications. Despite the fact that Kenney et. al's research was not placebo-controlled, their finding emphasizes the possible adverse effect of SSRIs on the mental health of PD patients seeking relief from their depressive symptoms. However, Maher et. al (2024) contrasts the perspective of Kenney et. al on SSRIs benefits towards depression treatment in PD, revealing that SSRIs are helpful in treating depression in PD, which is often comorbid but distinct from apathy. Although there is the possibility of SSRIs inducing apathy, experts maintain differing opinions on whether or not SSRI-induced apathy can worsen depression treatment, since depression and apathy are considered to be independent of one another. Szymkowicz et. al (2018) asserts that clinical presentation of psychiatric symptoms in Parkinson's can vary widely since degeneration of dopaminergic neurons in substantia nigra can differentially disrupt important emotion and cognitive brain circuits. The clinical diversity of Parkinson's disease and its psychiatric symptoms complicates the discussion of synthesizing a consensus on the most beneficial treatment towards depression, apathy, and psychiatric disorders comorbid with or resulting from Parkinson's disease in general.

The research of Szymkowicz et. al (2018) implores for future studies to investigate the relationship between mood symptoms and other meaningful outcomes in PD, such as activities of daily functioning, PD-MCI (mild cognitive impairment), or PD dementia status quality of life, and mortality. Additionally, there is a lack of research comparing apathy, especially SSRI-induced apathy, and its direct impact on depression symptomology and quality of life in patients with Parkinson's disease. It is vital to research the different manners in which SSRI-induced apathy can present itself in Parkinson's disease due to the wide variation of clinical presentation associated with the neurodegeneration involved in PD patients. Addressing whether SSRIs and the apathy it induces significantly worsens depression symptomology, quality of life, and treatment outcomes of Parkinson's disease patients can assist physicians, psychiatrists, etc. in modifying treatments for depression in PD patients. Understanding comorbid apathy and SSRIs effect on the quality of life of depressive PD patients allows for a more inclusive representation of PD patients with depression. Thus, this raised the research question I seek to answer: To what extent does SSRI-induced apathy significantly worsen depression treatment outcomes in Parkinson's disease patients? Based on the correlation between SSRIs and apathy, I hypothesize that SSRI-induced apathy significantly worsens the quality of depression treatment outcomes for PD patients.

## Methods

To analyze the extent to which SSRI-induced apathy worsens depression treatment outcomes for PD patients, it was essential to synthesize research using a qualitative review methodology, to examine the various components behind this complex clinical presentation in Parkinson's Disease. Using peer reviewed papers in the databases PUBMED and Proquest, I

decomposed my research question into three separate components: mechanisms of SSRIs as inducers of apathy in Parkinson's disease, the existence of apathy and depression as distinct disorders, and apathy's impact on the quality of life of PD patients.

**Table 1**

*Summary of Studies Utilized in Literature Review by Category*

| Category | Studies Unique to Category | Total Number of Studies Included | Number of Studies Excluded | Scales used (if applicable) | Date Range |
|---|---|---|---|---|---|
| SSRI-induced apathy in PD | 5 | 8 | 2 | BDI-11, AS, MADRS, HDRS, AES, GDS-15 | 2013-2025 |
| Apathy and Depression as Distinct Disorders | 1 | 6 | 1 | BDI-11, AS, GDS-15 | 2018-2024 |
| Possible impact of apathy and depression on PD patients' quality of life | 1 | 6 | 3 | BD1-11, AS, GDS-15 | 2018-2025 |

I confined my search range to 2018-2025, to express the rapidly evolving diagnostic criteria and clinical observations in Parkinson's disease related to apathy, SSRI-induced apathy,

depression symptoms, and their combined impact on quality of life of these PD patients. While at the same time, maintaining a 7-year window to encompass a greater amount of studies due to the specificity of all three components of my research question. An earlier study (Liu et. al, 2013) was included despite the 7-year window due to its role in establishing the efficacy of antidepressants for PD using placebo-controlled trials. The sample sizes of the studies I included that utilized clinical trials or a comprehensive review mainly revolved around adult patients with PD. I included 14 different studies and excluded 6 studies that were either before 2018, utilized a non-adult population of PD, or studies with incomplete data. Under the category analyzing mechanisms of SSRI-induced apathy in PD, I searched PUBMED and Proquest with keywords, “selective serotonin-reuptake inhibitors”, “SSRIs”, “apathy and antidepressants”, “SSRI-induced apathy”, “SSRIs and PD”, “SSRIs and Parkinson’s disease”, “antidepressant treatment in Parkinson’s disease”, “SSRIs and apathy in PD”, and “SSRIs and depression in PD”. For both the categories apathy and depression as distinct phenomena, and apathy’s impact on the quality of life of depressive PD patients, I limited questionnaire-based studies to those that utilized clinical scales Beck Depression Inventory 11 (BDI-11), Apathy Scale (AS), Hamilton Depression Rating Scale (HDRS) Montgomery-Asberg Depression Rating Scale (MADRS) Apathy Evaluation Scale (AES), MDS Unified Parkinson's Disease Rating Scale and Geriatric Depression Scale (GDS-15), to help control the heterogeneity inevitable in Parkinson’s disease and literature-review methodologies. To examine the distinguished traits and diagnostic criteria between apathy and depression, I utilized the same databases searching with keywords, “apathy”, “depression”, “apathy in Parkinson’s disease”, “depression in Parkinson’s disease”, “apathy and depression”, “apathy and depression in PD”, “depression treatment in PD”, “treating apathy in PD”, “diagnosing apathy in PD”, “depression diagnosis in PD” and “psychiatric symptoms in

PD". To research the possible impact on depression and quality of life in PD patients, I specified my search of literature using keywords "apathy in PD", "depression in PD", "antidepressants and apathy in PD", "SSRI-induced apathy in PD", "depression treatment in PD". After collecting sources related to the various keywords, I tracked the source, its authors, methodology details, key findings, and background information related to each source in a comprehensive Google Sheet.

## Literature Review

### Mechanisms of SSRIs as Inducers of Apathy in PD

Synthesizing research on apathy's association with antidepressant drugs using a systematic review through a PUBMED search, Masdrakis et. al (2023) establishes that SSRI-induced chronic increases of serotonin levels in the nucleus accumbens, due to 5HT-2c agonism, may lead to a down-regulation of dopamine turn-over in neurobiological structures associated closely with apathy. Using a double-blind placebo-controlled trial to understand how serotonin impacts neural mechanisms, Langley et. al (2024) affirms that abnormal response to reinforcing feedback has been observed in neuropsychiatric disorder, specifically major depressive disorder (MDD). . Liu et. al (2013) considers dopaminergic, noradrenergic, and serotonergic systems deficits are considered as primary etiological factors contributing to depression in PD. While antidepressants like SSRIs are intended to alleviate depressive symptoms by increasing serotonin levels, depression treatment for PD patients is made more difficult by the down-regulation of dopamine. To justify the prevalent use of SSRIs as depression treatment for PD patients, the journal *Pharmaceuticals* reinforces that SSRIs demonstrate a lack of potentially fatal adverse effects including harm to the heart and central nervous system,

primarily due to their restricted receptor antagonism (Zakaraya et. al, 2024). However, the research of Zakaraya et. al utilizes a comprehensive analysis of the pharmacodynamics and pharmacokinetics of psychiatric drugs. Clinicians use of the common view of SSRIs as “safe” may fail to take into account the complex neurodegeneration PD patients experience, impacting the acceptance and efficacy of antidepressants they may take.

Prevalence of severe antidepressant-induced apathy may be high, according to Masdrakis et. al (2023), an early study found that up to 80% of 15 patients with SSRI-induced sexual dysfunction also reported clinically significant emotional blunting, or inability to cry and express emotions. On the other hand, Masdrakis et. al (2023) substantiates that trials assessing SSRIs as a treatment for apathy pertaining to neurodegenerative disease other than PD have mostly failed to demonstrate a significant effect. Based on the impact of SSRIs on pathological emotional liability, a serotonergic hypothesis has been proposed that SSRIs may exert their therapeutic effect by elevating the threshold for feeling intense emotions and subsequently reducing emotional responsiveness. In a retrospective chart review using the Apathy Evaluation Scale, mean apathy scores were higher in the patients treated with SSRIs compared to those not treated with SSRIs out of 119 patients (Padala et. al, 2020). SSRIs are viewed by clinicians as both a possible inducer of apathy and a treatment. At the same time, unlike other neurodegenerative diseases, SSRIs have not been displayed in PD patients to be insignificant towards apathy, exacerbating the need for more extensive research on the significance of SSRI-induced apathy in Parkinson's disease.

The heterogeneity present in Parkinson’s disease etiology itself as well as within sample sizes places an obstacle to the ability of researchers to accurately determine how use of dopaminergic and pharmacological treatment impact apathy, Castrioto et. al (2025) reinforces

that effect of dopaminergic treatment on apathy has been inconsistent, depending on stage of disease, type of apathy, and is strongly influenced by placebo effect. Aguera-Ortiz et. al (2021) affirms that SSRIs are recommended by APA CPG and NICE, Spanish NHS, and EFNS/MDS-ES guidelines, but alerts on potential exacerbation of PD symptoms associated with SSRI uptake. Despite the recommendation of APA and other guidelines, Costello et. al (2024) asserts that dopamine agonists have been previously identified as effective towards treating disorders of motivation in PD, while role of dopaminergic therapies on motivation and mood are dependent on dopaminergic receptor profile, pharmacodynamics, brain region and progression of underlying PD pathology. While Costello and colleagues view dopamine agonists as effective towards treating motivational symptoms associated with PD, SSRIs remain the first choice of antidepressants towards PD. Thus, distinguishing between apathy and depression, or recognition of a comorbidity between the two, is essential for both the clinician and the PD patient to discover which pharmacological treatment is best suited for their psychiatric health.

**Apathy and Depression: Distinct Phenomena**

While apathy and depression are both significant psychiatric disorders associated with PD, Aguera-Ortiz et. al (2021) establishes that apathy has been wrongly considered a clinical criterion of depression exclusively, while efforts have been made for it to be distinguished as a standalone syndrome too in older patients with at least some neurological impairment. Using multivariable regression models to establish an association of depression with incident PD and regional brain volumes, Badenoch et. al (2024) in *The Journal of Neurology, Neurosurgery, and Psychiatry* discovered that depression is correlated with poorer PD prognosis including neurological outcomes (e.g., motor severity), disability, cognitive decline death. Thus, depression

itself already worsens prognosis and motor symptoms involved with PD, without consideration of apathy.

In PD, within characterizations of apathy and depression, multiple definitions and symptom descriptions mentioned the other. When researching the techniques of neuromodulation on apathy in PD, Maher et. al (2024) establishes that apathy within PD is correlated with lower premorbid educational attainment, depression, a longer disease course, etc. Likewise, for depression in PD, Costello et. al (2023) characterized depression to commonly include motivational symptoms such as apathy and anhedonia that occur in respectively 40% and 46% of patients. Szymkowicz et. al (2018) provides the basis for the association between apathy and depression in PD based on a sample of 138 non-demented patients experiencing PD exploring symptom dimensions between depression and apathy, revealing that loss of interest and pleasure is common in both depression and apathy which can make it difficult to differentiate between depression and apathy when that symptom is endorsed. On the contrary, due to these similarities, apathy is often underrecognized in neurological practice and misdiagnosed frequently, frustrating both patients and clinicians (Maher et. al, 2024). Similarities in clinical presentation thus complicate treatment options for apathetic, depressive, or comorbid PD patients. Defining and distinguishing apathy from depression in PD patients is crucial to preventing misdiagnoses and improving psychiatric treatment for apathetic PD patients.

However, apathy and depression symptomology maintain key differences. Patients with apathy can demonstrate lack of concern, depressed patients on the other hand display pathological self-criticism and negative outlook, symptoms usually absent in apathy (Masdrakis et. al, 2023). While the research of Masdrakis et. al was limited in the heterogeneity of its systematic review, their research indicates how apathy and depression remain distinct entities.

Aguera-ortiz et. al (2021) using a Delphi consensus completed by a panel of 37 physicians to homogenize diagnosis and treatment of depression in PD patients, affirms that serotonergic affective symptoms like hopelessness, sad mood, or suicidal thoughts would classify as key depression diagnostic criteria since they aren't distinctive features of apathy, which has a nonserotonergic origin. While Maher et. al (2024) argued that the common symptom of loss of pleasure can make it difficult to distinguish between apathy and depression, Masdrakis et. al (2023) contrasts revealing that patients can often distinguish their loss of interest as depression symptoms from apathy associated with SSRIs. Despite similarities between apathy and depression symptoms and clinical presentation, key differences including their serotonergic origins, patients ability to distinguish their loss of interest, etc. reinforce that apathy and depression are separate psychiatric disorders and must be clinically treated as such.

Investigating the presence of dissociable effects of dopaminergic meds on depression symptoms in PD in a sample of 412 newly diagnosed PD patients with a five-year follow-up, Costello et. al addresses a limitation of their research, emphasizing that depression is heterogeneous and etiologically complex with at least 256 unique symptom profiles that meet DSM-V criteria for diagnosis of major depressive disorder (Costello et. al, 2024). Costello and colleagues' 2024 study utilized the GDS-15 (Geriatric Depression Scale), one of many other depression diagnoses scales. This heterogeneity aggravates the process of diagnosing depression and apathy, making it nearly impossible for one scale to diagnose depression, the differing symptom profiles resulting in the creation of multiple depression scales.

**Apathy, Depression, and Possible Impact on Quality of Life**

Apathy induced by SSRIs and present in PD has the potential to worsen depression treatment by significantly contributing to cognitive dysfunction. Connors et. al (2023) in the journal *International Psychogeriatrics* conducted a longitudinal study examining neuropsychiatric symptoms such as depression and apathy in patients with mild cognitive impairment, showcasing that patients with apathy showcased worse function, increased severity of dementia, depression, overall neuropsychiatric symptoms, and caregiver burden than patients with no apathy. Thus, Connors and colleagues emphasizes the declining quality of life associated with apathy and declining cognitive function. Szymkowicz et. al (2018) establishes that both apathy and depression have been shown to negatively impact cognition in PD, with depression most consistently associated with worse delayed episodic memory and executive functioning, and apathy most consistently associated with worse executive function. A 4-year longitudinal study by Petkus and colleagues could detect that cognitive decline correlates with a subsequent increase in anxiety and depression symptoms (Aguera-ortiz et. al, 2021). When evaluating prognostic implications of depression in Parkinson's disease, Badenoch et. al (2024) posed that greater depression symptom severity among individuals with PD were associated with reduced grey matter volume in 18 brain regions, distributed, bihemispherically and predominantly comprising subcortical structures including thalamus and amygdala and several cortical regions. Thus, the presence of apathy alongside depression in Parkinson's disease patients has the ability to stimulate a cycle of worsening depression symptoms through poorer cognition, already weakened due to neurodegeneration in PD.

Castrioto et. al (2025) investigated the evolution of apathy symptoms of 86 de novo Parkinson's disease patients after dopaminergic treatment and demonstrates that the group of patients with baseline apathy had higher scores of fatigue at disease onset and follow up,

possibly due to apathetic patients complaining easily of fatigue. Dopaminergic treatment is used as an antidepressant for PD patients, displaying the likelihood of antidepressants, like SSRIs, to worsen apathetic symptoms and debase depression treatment. The interest-activity' symptom dimension of apathy in depression including loss of interest, diminished activity, difficulty decision-making, and fatigue has been correlated with poor outcome of antidepressant treatment in large prospective clinical studies (Costello et. al, 2024). Thus, altering dopamine levels and functioning in the brain can exacerbate apathetic symptoms in depression, despite the role of antidepressants like SSRIs to alleviate depression symptom severity.

## Implications

Ultimately, the qualitative research I synthesized was able to support my hypothesis that SSRI-induced apathy can significantly worsen depression treatment outcomes for Parkinson's disease patients. Multiple studies identified a significant relationship between dopaminergic mechanisms and severity of depression and apathy in PD. In turn, SSRIs' downregulation of dopamine impacts in neural mechanisms like the ventral striatum and nucleus accumbens impacting motivation can stimulate development of apathy in depressive PD patients. I sought to evaluate how the emergence of apathy from antidepressants SSRIs impacts the existing depression symptoms Parkinson's disease patients were utilizing SSRIs as treatment for. The co-occurrence of apathy and depression as a result of SSRI-induced apathy can stimulate a cycle of worsening depression and apathy symptoms in PD patients.

SSRIs have historically been a common and first-line pharmacological treatment for depression in Parkinson's disease. A 2024 study by Zakaraya and colleagues defended the use of SSRIs, reinforcing that restricted receptor antagonism has allowed for a lack of potentially fatal

adverse effects in SSRIs allowing them to remain in use. At the same time, studies by Kenney and colleagues, Masdrakis and colleagues, Liu and colleagues, etc. have condemned the use of SSRIs in Parkinson's disease due to their possible stimulation of symptoms associated with apathy. On the other hand, dopaminergic neurons in Parkinson's disease displays a unique neurodegeneration in comparison to depression as a standalone disorder and in other diseases, indicating that treating depression in Parkinson's disease must be tailored to its differential motivational functioning.

With a presence of both depression and apathy, quality of life for Parkinson's disease patients may worsen due to a greater severity of both apathy and depression symptoms. Studies by Connors and colleagues, Szymkowicz and colleagues, and Aguera-ortiz and colleagues have demonstrated a theme of an inverse relationship between cognitive functioning and apathy/depression in Parkinson's disease. Thus, the presence of SSRI-induced apathy can exacerbate cognitive dysfunctioning in Parkinson's disease. A 2025 study by Castrioto and others revealed a worsening of both non-motor symptoms and motor symptoms in a longitudinal assessment of apathy in Parkinson's disease. SSRI-induced apathy worsens existing motor symptoms, may intensify depression symptoms, exacerbate cognitive dysfunctioning. Relationships between apathy, SSRI treatment, depression, and cognitive functioning in Parkinson's disease exemplifies a cyclical nature of a worsening of psychiatric symptoms, contributing to a poorer quality of life for PD patients. Ramifications of SSRI-induced apathy in PD patients emphasizes the need for clinicians to develop a more comprehensive diagnostic criteria for determining depression treatment and diagnoses in PD patients, to better evaluate appropriate treatment plans for depressive and apathetic PD patients. However, the variance in clinical presentation of Parkinson's disease and depression limits the ability to maintain a homogeneous treatment plan. Despite the difficulty this heterogeneity creates, synthesis of research on SSRI-induced apathy, differences between apathy and depression, and apathy and

depressions contributions to quality of life in PD patients signifies the necessity of recognizing apathy in PD patients in clinical practice. Depression treatment for PD patients is composed of a multitude of different factors, revealing that clinicians treating PD patients should maintain close attention to recognize the unique clinical presentation of neuropsychiatric and motor symptoms within each patient.

**Limitations**

Due to the use of a qualitative synthesis of existing research on SSRI-induced apathy in depressive PD patients, my research involves a degree of heterogeneity. I was unable to directly investigate how SSRI-induced apathy can impact depression treatment outcomes in a singular sample size of PD patients with real human involvement. Additionally, the sample sizes and trial duration of the studies I reviewed varied. In attempts to limit heterogeneity, I limited the behavioral scales determining apathy and depression in PD to only 4 different scales. While, the presence of shared symptoms of depression and apathy in Parkinson's disease patients may overrepresent apathy and depression scores in these behavioral diagnoses scales. However, I found that qualitatively analyzing various existing studies related to SSRI-induced apathy and depression treatment in PD patients allows me to better examine the various complex clinical factors that went into my research question.

**Future Research**

Considering my findings, I implore future Parkinson's disease research to confine and homogenize diagnostic criteria for depression and control for apathetic symptoms. Since, existing therapeutic interventions for depression in PD have been neither definitive or specific (Aguera-ortiz et. al, 2021). I would encourage for my research question to be applied to a more

homogenous population of Parkinson's disease patients experiencing depression symptoms. Researching the most acceptable antidepressant treatment for Parkinson's disease must include the use of placebo-controlled trials. The placebo effect in Parkinson's disease is prevalent and related to release of dopamine in dorsal and ventral striatum found in PET studies using dopamine D2 receptor antagonist raclopride (Liu et. al, 2013). Determination of severity of apathy and depression in this population of PD patients could be accomplished by licensed psychiatrists in Parkinson's disease. Exploring SSRI-induced apathy and depression in Parkinson's disease patients within a homogeneous population of PD patients using a more direct clinician involvement in diagnosis limits the exaggerated scores involved with questionnaire-based studies utilizing flawed apathy and depression score scales.

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