Effect of Intranasal Insulin for Anosmia and Hyposmia in Parkinson’s Patients

Eden Anonye

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EFFECT OF INTRANASAL INSULIN FOR ANOSMIA AND HYPOSMIA IN PARKINSON’S PATIENTS

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

July 2023

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ABSTRACT

Olfaction impairment is one of the earliest nonmotor symptoms of Parkinson’s disease. Olfaction disorders in patients with Parkinson’s disease can range from hyposmia, a reduction in smell ability, to anosmia, a complete loss of smell. Regardless of severity, olfaction loss can result in decreased well-being and mood disorders. However, there is no approved management for anosmia or hyposmia secondary to Parkinson’s disease. Insulin is hypothesized to modulate olfactory neuron regeneration in patients with post-infectious hyposmia, but its effects have not been studied in Parkinson’s patients. Using a randomized controlled trial design, we seek to determine whether eight weeks of daily application of intranasal insulin results in a significant improvement in olfaction performance over baseline in Parkinson’s patients with a 6-month minimum history of anosmia or hyposmia. The results from this study could provide an evidence-based treatment option for this bothersome non-motor symptom, for which there are no treatment options.
Chapter I: Introduction

1.1 Background

Parkinson’s disease (PD) is a progressive, neurodegenerative movement disorder characterized pathophysiologically by a decrease in dopaminergic neurons within the substantia nigra pars compacta resulting in several motor function abnormalities. PD is the second most common neurodegenerative disorder and primarily affects individuals over the age of 60. Recent epidemiological data suggests an increasing prevalence of PD in the United States. As the United States’ aging population continues to grow, the number of PD diagnoses is projected to rise, thus amplifying overall disease burden.

Motor manifestations of PD include resting tremors, rigidity, bradykinesia, postural instability, and gait dysfunction. Patients often experience a variety of non-motor features including weight loss, constipation, drooling, sleep disturbances, mood disorders, and apathy which can precede motor symptom onset by multiple years. Olfaction impairment is a common prodromal symptom and as a result, many patients display this dysfunction at the time of primary motor presentation.

PD-associated olfaction dysfunction can range from anosmia, a complete lack of smell ability, to hyposmia, a reduction in smell ability. Anosmia and hyposmia are clinical diagnoses that can be used to support the diagnosis of PD, but these disabilities are frequently unaddressed in PD treatment plans given the lack of available treatment. This is not benign; patients with anosmia and hyposmia report decreased quality of life, decreased food enjoyment with subsequent weight loss, and an inability to detect potentially toxic substances such as rancid food, gas leaks, and smoke. One study surveyed 265 PD patients to determine the most troublesome PD associated symptoms and found that olfaction dysfunction was ranked as the 2nd...
most bothersome non-motor symptom among early PD patients. Participants in this study only cited pain as a more burdensome non-motor symptom. This result is consistent with other studies which have found olfaction dysfunction to be a considerable source of psychological burden and social insecurity.

There is no current pharmacologic treatment for olfaction dysfunction secondary to PD. Multiple studies have investigated potential pharmacologic interventions, such as dopamine agonists, for PD-associated anosmia and hyposmia, but none have been able to significantly improve olfactory function in PD study participants. One potential reason for the lack of effective treatment is that research investigating the exact pathophysiology underlying olfactory dysfunction in PD is ongoing. It is currently hypothesized that pathologic accumulation of alpha-synuclein protein in the olfactory regions of the brain leads to olfactory neuron degeneration and the subsequent impairment in olfactory function seen in PD.

The olfactory bulbs, located on the inferior surface of the cerebral hemispheres, contain the highest density of insulin receptors in the brain and it is believed that insulin is necessary for olfactory mucosa regeneration after injury. This information has been the foundation for current otolaryngologic research exploring the use of intranasal insulin in olfaction disorders. Recent studies have reported that the use of intranasal insulin is effective in restoring olfactory performance in individuals with post-infectious anosmia or hyposmia. Although the aforementioned studies were not designed to study the use of insulin for olfaction disorders secondary to PD, the studies’ conclusions can be used as foundation for similar research within a PD-specific population.
1.2 Statement of the Problem

Despite the documented impact of olfactory dysfunction in PD, effective pharmacologic interventions are unavailable. Olfaction dysfunction is a large source of morbidity for this patient population with its effects contributing to the depressive symptoms many PD patients experience\(^5\). It is estimated that the prevalence of significant hyposmia in early sporadic PD is as high as 90\(^%\)\(^1\). Despite this high prevalence, research with adequate sample sizes investigating potential treatment options for olfaction disorders in PD patients is lacking. Intranasal insulin has been proposed as a potential treatment option for olfaction disorders for those without neurodegenerative disorders, but this concept has not yet been studied within the PD population.

1.3 Goals and Objectives

The primary goal of this study is to investigate the efficacy of intranasal insulin for olfaction disorders among individuals with anosmia or hyposmia secondary to PD. This proposed study will utilize a double-blind randomized placebo-controlled trial format to investigate this question. Efficacy will be measured by the mean baseline change in olfaction performance among Parkinson’s patients with a 6-month or more history of anosmia or hyposmia, as quantified by a TDI (threshold, discrimination, and identification) score (comprehensive score of smell abilities obtained by use of Sniffin’ Sticks). Quality of life, quantified by Parkinson’s Disease Questionnaire (PDQ-39) scores, will be a secondary variable measured at baseline and upon study conclusion.

1.4 Research Question

Among Parkinson’s patients with a 6-month or greater history of hyposmia or anosmia, is eight weeks of once daily application of intranasal insulin, compared to intranasal saline, associated with a significant improvement in olfaction performance as measured by TDI scores?
1.5 Hypothesis

Among Parkinson’s patients with a 6-month history of hyposmia or anosmia, the mean baseline change in olfaction performance among the two intervention groups, receiving eight weeks of once daily application of either 40 or 80 international units (I.U.) of intranasal insulin, will be statistically different from the mean baseline change in olfaction performance within the control group receiving intranasal saline.

1.6 Definitions

Anosmia: Complete loss of smell abilities.

Hyposmia: Reduction of smell abilities.

TDI: Comprehensive sum of odor threshold, odor discrimination, and odor identification scores, obtained via use of Sniffin’ Sticks, allowing for assessment of an individual’s olfactory abilities.

Sniffin’ Sticks: A validated olfactory screening test kit allowing for the classification of an individual’s nasal chemosensory performance using pen-like odor dispensing devices.

Parkinson’s Disease Questionnaire (PDQ-39): Self report questionnaire with 39 questions relating to mobility, activities of daily life, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. Scores from the questionnaire are used to assess quality of life for those with Parkinson’s disease.
1.7 References

Chapter II: Literature Review

2.1 Introduction

A comprehensive literature review of PubMed and Ovid MEDLINE was conducted between June 2022 and July 2023. Various combinations of the following keywords were used to find applicable English language articles: Parkinson’s disease, idiopathic Parkinson’s, anosmia, hyposmia, olfaction disorders, intranasal insulin, safety, treatment, efficacy, Sniffin’ Sticks, TDI score, quality of life, and Parkinson’s disease questionnaire.

2.2 Review of Existing Data

2.2.1 Olfaction Disorders in Parkinson’s Disease

Olfactory dysfunction is a characteristic and well-documented non-motor symptom in PD. Multiple studies have consistently demonstrated the high prevalence of olfactory impairment among individuals with PD, with recent data estimating that >95% of PD patients have significant olfaction impairment at the time of initial presentation\(^1\). The severity of the olfactory deficit can range from anosmia, complete loss of smell, to hyposmia, reduced sense of smell. Studies investigating the relationship between anosmia and hyposmia in PD have also concluded that olfactory impairment often occurs in early stages of the disease, most often preceding the onset of classic PD motor symptoms by several years\(^1,2\). These results align with the findings of a more recent study focused on clinical markers used in prodromal PD diagnosis. This study reported a positive likelihood ratio of 6.4 for olfactory loss, indicating that this symptom serves as a moderately strong diagnostic indicator of prodromal PD\(^3\).

One of the histologic hallmarks of PD is the abnormal neuronal accumulation of alpha-synuclein protein\(^4\). The underlying pathophysiology of olfactory dysfunction in PD is believed to
involve aggregates of this same protein within the olfactory bulb and olfactory pathways within the brain\textsuperscript{4}. Human brain autopsy studies have revealed that olfactory regions and lower brain structures may be affected prior to involvement of the substantia nigra in PD, which likely contributes to the olfactory impairments observed in PD patients\textsuperscript{5}.

2.2.2 Proposed Treatments for Anosmia and Hyposmia in PD

Currently, there are no effective pharmacologic treatment options for anosmia and hyposmia secondary to PD despite ongoing efforts. Dopaminergic neuron degeneration in the substantia nigra is a main cause of PD and thus dopamine metabolic precursors and agonists are standard medications used for PD management. Given the relationship between dopamine deficiency and the development of classic PD symptoms, one study proposed that treatment with apomorphine, a dopamine agonist, could treat PD-associated anosmia and hyposmia. However, results from this study found that apomorphine therapy was unsuccessful in improving olfactory thresholds among 12 PD participants\textsuperscript{6}. These results align with another study’s findings which concluded that the presence of hyposmia in PD is independent of the number of dopaminergic cells within the olfactory bulbs\textsuperscript{7}. Thus, while dopamine therapy is effective in treating the motor manifestations of PD, its uses are limited for treatment of anosmia and hyposmia secondary to PD.

Cholinesterase inhibitors, commonly used in the treatment of cognitive impairments in conditions like Alzheimer’s disease, have been considered in the context of olfactory dysfunction in PD. These medications including donepezil, rivastigmine, and galantamine, aim to enhance cholinergic neurotransmission and are hypothesized to have potential in improving olfactory function in PD patients. One study found that central cholinergic deficits are strong determinants of hyposmia in PD\textsuperscript{8}. Results from this study have been extrapolated to propose that
supplementation with cholinergic agonists and/or cholinesterase inhibitors could be effective in treating PD associated olfaction dysfunction. However, studies investigating this idea have yet to be conducted.

Nicotine, a cholinergic agonist, is believed to provide a protective effect against PD associated olfaction dysfunction. Moreover, current smoking status and former smoking history have been associated with negative likelihood ratios of 0.51 and 0.91, respectively, in prodromal PD diagnoses, indicating a potential protective role of smoking against PD development. Interestingly, related retrospective studies have found that PD patients with a history of smoking exhibit better olfaction abilities than PD patients without a smoking history. While this association has been revealed in multiple independent retrospective studies, the use of nicotine for treating PD-associated anosmia and hyposmia remains limited due to the absence of a definitive causal relationship between nicotine and olfaction improvement in PD patients. Additionally, it is essential to consider that while nicotine may confer benefits for olfaction in PD, the negative health effects associated with smoking, such as increased risk of cardiovascular disease and malignancy, must be considered. Therefore, use of nicotine and/or smoking as treatment for PD-associated anosmia and hyposmia should be approached with caution, and alternative strategies that minimize potential harm should be explored. Further research is needed to better understand the interplay between nicotine and olfaction in the PD population.

More recent studies have investigated potential non-pharmacologic treatment options for PD-associated olfaction dysfunction. In a 2013 prospective study, it was found that olfactory function significantly improved among 35 PD patients who were allocated to receive 12 weeks of olfactory training via twice-daily exposure to 4 different odors. While this result suggests that olfaction function is capable of recovery after PD associated neurologic injury, the study is
limited as the design was non-blinded and investigators were unable to conclude if the effects of the training were long-lasting.

Deep brain stimulation (DBS), a neurosurgical procedure in which implanted electrodes deliver electrical impulses with the goal of modulating brain activity, has been extensively studied as a treatment modality for PD-associated olfaction dysfunction. In a study conducted by Hummel et al, active DBS therapy to the subthalamic nucleus demonstrated significant improvements in odor discrimination among 11 patients with hyposmia secondary to PD. Several other studies have reported similar findings, suggesting the efficacy of DBS in enhancing olfactory function in PD patients with anosmia or hyposmia. Despite these positive results, DBS is an invasive procedure associated with severe adverse effects including seizure, infection, and stroke. Additionally, our knowledge of DBS therapy’s impact on olfactory abilities in PD patients is limited by the lack of long term follow up periods in these studies.

2.3 Mechanism of Action of Intranasal Insulin

Insulin, a hormone used in glucose regulation, has emerged as a potential modulator of olfactory function. Studies have demonstrated that insulin receptors are widely expressed throughout the human brain, but the olfactory bulb contains the highest density of insulin and insulin receptors in the brain, suggesting a direct involvement of insulin in olfactory processes and signaling. Impaired insulin signaling is believed to contribute to PD progression and neurodegeneration, while insulin’s neuroprotective effects are hypothesized to be essential for olfactory mucosa repair and maintenance. Many studies have corroborated this idea, demonstrating that intranasal insulin is effective in improving olfactory performance.

One 2015 investigation investigated the effects of intranasal insulin on 10 participants with post-infectious anosmia and found that odor threshold and sensitivity improved by 60%,
compared to only 28% in the intranasal saline control group, when olfactory performance was reassessed 30 minutes after intranasal insulin administration. In a 2018 double-blind randomized controlled trial, investigators explored the effects of twice weekly application of insulin gel foam endoscopically placed in the olfactory cleft of study participants with mild to severe hyposmia. The results of this experimentation showed that the mean scores of odor identification and smell threshold were significantly higher in the insulin-treated group compared to the saline-treated control group after 4 weeks (p=0.01). While these studies examining the effects of intranasal insulin focused on patients with anosmia and hyposmia unrelated to PD, the suggested mechanism of action, involving insulin’s regenerative properties on olfactory mucosa, suggests its potential applicability in the PD population.

After an extensive literature review, we are not aware of any study that has specifically explored the effects of intranasal insulin on PD-associated anosmia and hyposmia. The research on the use of intranasal insulin in PD has primarily focused on its application in treating other PD symptoms including verbal fluency, apathy, cognition, and motor function. Despite limited sample sizes and data, results from these studies have demonstrated that intranasal insulin may be effective in improving functional impairments in PD without risk of severe adverse effects including hypoglycemia.

2.4 Review of Relevant Methodology

2.4.1 Study Design, Intervention Administration, and Safety

Due to the lack of previous research examining the effects of insulin on olfactory disorders in PD, we based our methodology on a pilot study which explored the use of intranasal insulin on other non-motor symptoms of PD including cognition. Our proposed study is a double-blind, randomized controlled trial. After enrollment, participants will be randomized to
one of 3 interventions: placebo/intranasal saline, 40 I.U. of regular intranasal insulin (Novolin-R), or 80 I.U. of regular intranasal insulin (Novolin-R). Participants will then administer their intranasal intervention once daily for a total of 8 weeks.

We selected intranasal insulin administration over intravenous or subcutaneous routes due to its simplicity, non-invasiveness, teachable nature, safety profile, intracranial bioavailability, and pharmacokinetics. Intranasal administration allows for rapid passage of insulin through the blood-brain barrier allowing direct delivery to the brain within minutes, which is otherwise not achievable with other routes of administration.\(^{24}\)

In order to explore the potential dose-dependent response of intranasal insulin on olfactory performance, we included a second intervention dose of 80 I.U. in our study. This choice was influenced by a separate study that examined the impact of intranasal insulin on olfactory perception in normosmic individuals and found a significant dose-dependent relationship between intranasal insulin and olfaction performance.\(^{25}\)

Although insulin is a widely used medication, it is important to recognize that insulin is associated with risks. Excessive administration of insulin can lead to hypoglycemia, a condition associated with various severe consequences including palpitations, paresthesia, seizure, coma, and death. We justified a daily dosing intranasal insulin protocol based on a retrospective review of 832 participants which found that extended use (up to 9 years) of daily intranasal insulin did not result in hypoglycemia or severe adverse effects.\(^{26}\) The most commonly reported adverse effect was nasal irritation which is to be expected given the administration route.\(^{26}\)

2.4.2 Selection Criteria and Study Population

Our study population will involve individuals between the ages of 18 and 90 who have a provider documented diagnosis of idiopathic PD, characterized by the distinctive sign of
bradykinesia, along with the presence of either resting tremor or rigidity, without any other known or suspected secondary causes of Parkinsonism. These diagnostic criteria for PD are in accordance with the guidelines provided by the Movement Disorder Society (MDS) and will be confirmed by a study associated movement disorders fellowship trained neurologist prior to participant enrollment. Additionally, study participants must be on a stable anti-PD medication dose for at least 4 weeks prior to study enrollment with the expectation of no further dosing changes over the study duration.

Due to the novelty of our proposed study, there is limited data from related studies that can serve as reference for our study design, but the selection criteria for our proposed study largely align with the selection criteria in comparable studies. In a prospective, controlled, non-blinded study which investigated the effects of olfactory training on olfactory performance in PD patients, selection criteria were designed to include participants 18 years or older with a diagnosis of PD, as defined by UK Brain Bank criteria, and were on a stable anti-PD medication regimen for at least 4 weeks prior to study enrollment. In this study, participants were excluded if they had an identifiable cause of their PD or evidence of atypical PD disorders. We defined our selection criteria to include participants on a stable anti-PD medication regimen, like the prospective non-blinded study, to prevent potential confounding.

During our comprehensive literature review of studies researching potential treatments for olfactory dysfunction in PD, we observed that selected studies did not consistently specify a timeline or duration for olfactory dysfunction in their selection criteria. For example, a study investigating the effects of DBS on PD-associated hyposmia and constipation assessed PD participants for hyposmia after enrollment. Surprisingly, the results showed that only 54.7% of the PD study participants met the diagnostic criteria for hyposmia.
In a separate DBS study, investigators arranged for study participants to undergo evaluation by an otolaryngologist and subsequently conduct a baseline olfaction test following enrollment\textsuperscript{14}. However, specific details describing the otolaryngologist’s evaluation and how olfactory deficit severity was determined in participant selection were not provided in the study’s published article\textsuperscript{14}. Review of additional studies exploring interventions for PD-associated olfaction dysfunction did not provide any additional insight into methodology to best define baseline olfaction deficits in inclusion criteria.

Given the variation in how baseline olfaction deficit was defined in exiting studies, we designed our own inclusion criteria to include participants with a documented 6-month minimum history of anosmia or hyposmia considered to be secondary to PD. This timeframe was based on a study that investigated smell and taste loss recovery in COVID-19 patients, where it was observed that the majority of study participants (88\%) reported recovery within 2 months\textsuperscript{28}. By implementing a minimum duration of 6 months of olfaction deficit, we aimed to account for potential olfactory recovery if the deficit was associated with a non-PD etiology.

Our study inclusion criteria also specifies that participants must undergo the Montreal Cognitive Assessment (MoCA), a screening tool to assess for cognitive impairment, and obtain a minimum score of 10 prior to enrollment. This requirement aims to minimize the impact of cognitive changes on the participant’s ability to perform the olfaction test effectively. Additionally, considering the variability in PD symptom severity among individuals, we plan to utilize the Hoehn and Yahr Scale to determine participants’ PD associated functional disability. To prevent severe disability from influencing study outcomes, participants must have a Hoehn and Yahr Scale score less than or equal to 3.
The decision to implement a minimum MoCA score of 10 and a maximum Hoehn and Yahr score of 3 in the inclusion criteria was based on an ongoing study investigating the effects of intranasal insulin on PD-associated cognition, mood, apathy, and motor function\textsuperscript{29}.

Participants will be excluded if they fail to meet the metrics stated above. For the full list of inclusion and exclusion criteria, please refer to Chapter 3.

\textbf{2.4.3 Outcome Measure}

The primary outcome in our proposed study will be change in olfactory performance measured from enrollment (baseline) to interventional conclusion (8 weeks) and follow up (16 weeks). Olfaction performance will be measured via use of Sniffin’ Sticks which are a validated and commonly used olfactory screening test kit allowing for the classification of an individual’s nasal chemosensory performance using pen-like odor dispensing devices\textsuperscript{30}. The Sniffin’ Sticks test kit is comprised of 3 olfactory tests which assess an individual’s odor threshold, odor discrimination, and odor identification abilities. Individual scores from threshold (T), discrimination (D), and identification (I) tests can be summed to obtain a TDI score, a comprehensive assessment of olfactory performance \textsuperscript{30}. Scores are then compared to normative values established for each gender and 4 age groups for percentile data \textsuperscript{30}. TDI scores less than or equal to 16.5 are defined as functional anosmia. TDI scores above 30.5 are defined as normosmia, or normal olfactory function. Scores between 16.5 and 30.5 are defined as hyposmia. Instructions for conducting the threshold, discrimination, and identification tests and calculating associated scores is provided with the Sniffin Sticks kit.

A literature review of studies investigating potential therapies for PD-associated olfaction deficits revealed that in addition to Sniffin’ Sticks, the Connecticut Chemosensory Clinical Research Center (CCCRC) and the University of Pennsylvania Smell Identification Test
(UPSIT) are commonly used olfaction measurement tools in anosmia and hyposmia research. In our study, we opted to utilize Sniffin’ Sticks as the preferred assessment tool over the CCCRC and UPSIT tests. The selection of Sniffin’ Sticks was driven by the consideration that this test provides a more extensive range of data points as compared to the other tests. Sniffin’ Sticks consists of three subtests that collectively provide a comprehensive score reflecting the participant’s olfactory performance. In contrast, the CCCRC test comprises 2 subtests, while the UPSIT test focuses on a single identification test. By employing Sniffin’ Sticks, we aim to obtain a more comprehensive and detailed assessment of olfactory function in our study participants.

The second outcome in our study will be change in study participants’ quality of life from enrollment (baseline) to interventional conclusion (8 weeks) and follow up (16 weeks). Quality of life will be assessed via use of the Parkinson’s Disease Questionnaire (PDQ-39). The PDQ-39 is a self-report questionnaire with 39 questions relating to mobility, activities of daily life, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort associated with PD-related morbidity. Scores obtained from the questionnaire are commonly used to assess the quality of life for those with Parkinson’s Disease.

It is well-established that olfaction disorders can significantly impact an individual’s quality of life. Therefore, we hypothesize that an improvement in olfactory function would have a positive effect on overall participant well-being. By measuring changes in quality of life, we can gain insights into the experiences and perceptions of study participants. This assessment can also serve as a proxy for evaluating participant satisfaction, an important factor in predicting long-term adherence to the intervention.
2.4.4 Sample Size Calculations

The sample size calculation in our proposed study was based on three studies whose primary outcome was change in olfaction performance. There are no existing studies exploring the use of intranasal insulin in a PD population so we calculated an effect size of 16.5% by averaging the relative effects, of 31% and 2.2%, from Rezaeian’s and Schopf’s studies which investigated the effects of intranasal insulin on olfaction performance in a non-PD population\textsuperscript{21, 22}. Using the 16.5% effect size and the control group’s mean TDI score of 17.2 ± 4.8 from Haehner’s study on changes in olfactory performance after 12 weeks of olfactory training in a PD population, we calculated a population mean of 20.04 for the intranasal insulin group\textsuperscript{12}. There is an increased risk of a type 1 error in our proposed study since olfaction function will be measured at multiple time points. So, we used the Bonferroni approach to calculate an alpha level of 0.010 to negate this effect. Based on these calculations, our study will require a total of 207 patients, split evenly between 2 intervention groups and a single control group, to detect a 16.5% effect size with 80% power and an alpha level of 0.010. However, to account for a 20% loss to follow-up, we will aim to recruit 250 participants. For additional information on our sample size, please refer to Chapter 3 and the accompanying calculation in Appendix D.

2.5 Confounding Variables

Our literature review revealed several potential confounding variables which threaten the validity of our proposed study. Olfaction dysfunction is a common non-motor symptom that can precede an official PD diagnosis by 4.5 years\textsuperscript{33}. PD duration plays a role in the progression of olfactory impairment, as patients with longer disease duration are suspected to have more pronounced olfaction deficits\textsuperscript{33}. Failure to account for disease duration as a confounding factor in
PD olfaction research could lead to misleading results and skewed interpretations. Literature review revealed that many PD focused research projects account for disease duration by measuring this variable at baseline between intervention and control groups\textsuperscript{12, 14-16}. To account for disease duration as a potential confounding variable in our study, we will record disease duration at baseline between the control group and intervention groups to ensure adequate randomization. If randomization does not properly balance this baseline characteristic across the 2 intervention and single control groups, we will use linear regression to perform multivariate analysis to account for any potential confounding effects.

PD functional impairment and symptom severity, as assessed by measures such as the Hoehn and Yahr Score and the Unified Parkinson’s Disease Rating Scale (UPDRS), are other important confounding variables frequently addressed in existing PD olfaction research. Olfaction dysfunction in PD can range in severity, and its impact on patients’ quality of life can vary accordingly. As PD is a progressive disorder, longer disease duration often leads to greater functional impairment and higher symptom severity, potentially exacerbating olfaction dysfunction\textsuperscript{33}. In previous relevant studies, these scores were calculated at baseline to ensure appropriate distribution between intervention and control groups \textsuperscript{12, 14-16}. To address these potential confounding variables, we will assess PD functional impairment and symptom severity at baseline and aim to control for them through randomization procedures.

COVID-19 infection, nasal polyps, sinusitis, rhinitis, and nasal or sinus deformity are all potential etiologies of olfaction deficits\textsuperscript{34}. Failure to account for these conditions in our proposed study may introduce confounding factors that could impact the interpretation of our data. Similar to the reviewed studies, our proposed study will account for these confounders by excluding participants diagnosed with any of these conditions.
2.6 Conclusion

Despite numerous investigations into potential interventions, our literature review revealed a lack of effective pharmacologic treatment options for PD patients with anosmia and hyposmia. Several investigations have shown the promising results of intranasal insulin on olfactory loss, but this idea has yet to be studied within a PD specific population. Our proposed study aims to bridge this current literature gap by investigating the use of intranasal insulin in individuals with anosmia and hyposmia secondary to PD.
2.7 References


Chapter III: Study Methods

3.1 Study Design

This study will be a double-blind, randomized controlled trial. After enrollment, participants will be randomized to one of 3 interventions: placebo/intranasal saline, 40 I.U. of intranasal insulin, or 80 I.U. of intranasal insulin. Study participants will present to the test site for the first dose administration then will self-administer the intervention once daily for a total of 8 weeks. Participants will administer their assigned intervention one hour after their daily scheduled PD medication. Participants will have olfaction performance tests conducted at baseline, 8 weeks after intervention onset (time of final intervention dose), and 8 weeks after final intervention dose to observe for outcome permanence. Participants, research medical staff, and study evaluators will be blinded to participant allocation.

3.2 Study Population and Sampling

Study participants must be between 18-90 years old with a diagnosis of idiopathic PD. Eligible participants must have a minimum 6-month history of hyposmia or anosmia secondary to their PD. Participants will be excluded from the study if they have any of the following: insulinoma, type 1 or type 2 diabetes, dementia, anosmia or hyposmia secondary to COVID-19 infection, nasal polyps, acute or chronic sinusitis, current COVID-19 or upper respiratory infection, nasal deformity, non-allergic rhinitis, or any other probable etiologies for their olfaction deficits. Current smokers, pregnant individuals, and non-English speakers will also be excluded from the study. Participants will be disenrolled if they develop COVID-19 anytime during the study duration. Participants must be able to provide consent, self-administer the intranasal intervention, and attend scheduled follow ups for participation.
Potential participants will be identified via use of Yale Neurology’s electronic medical record (via chart review following IRB approval). If potential participants satisfy inclusion criteria and do not meet exclusion criteria, their providers will be contacted and asked to inform their patients about the study. If the patient is interested in participating, the provider can provide the patient with study enrollment contact information. Participants will complete consent paperwork prior to enrollment. Participants will receive a $100 Amazon gift card for intervention and follow-up adherence.

Table 1: Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>• Between 18-90 years old</td>
<td>• Age &lt;18 years old</td>
</tr>
<tr>
<td>• Diagnosis of Idiopathic Parkinson’s disease in accordance with Movement Disorder Society diagnostic criteria</td>
<td>• Age &gt;90 years old</td>
</tr>
<tr>
<td>• Provider documented ≥ 6-month history of anosmia or hyposmia secondary to Parkinson’s Disease</td>
<td>• Current smokers</td>
</tr>
<tr>
<td>• On a stable anti-Parkinson’s disease medication regimen and dose for 4 weeks prior to enrollment</td>
<td>• Non-English speakers</td>
</tr>
<tr>
<td>• Minimum Montreal Cognitive Assessment (MoCA) score of 10</td>
<td>• Pregnant individuals</td>
</tr>
<tr>
<td>• Hoehn &amp; Yahr stage less than or equal to 3</td>
<td>• Diagnosis of insulinoma</td>
</tr>
<tr>
<td></td>
<td>• Diagnosis of type 1 or type 2 diabetes mellitus</td>
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<tr>
<td></td>
<td>• Diagnosis of dementia</td>
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<tr>
<td></td>
<td>• Diagnosis of nasal polyps</td>
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<tr>
<td></td>
<td>• Diagnosis of acute or chronic sinusitis</td>
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<td></td>
<td>• Diagnosis of nasal deformity</td>
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<tr>
<td></td>
<td>• Diagnosis of non-allergic rhinitis</td>
</tr>
<tr>
<td></td>
<td>• Current COVID-19 infection</td>
</tr>
<tr>
<td></td>
<td>• Current upper respiratory infection</td>
</tr>
<tr>
<td></td>
<td>• Unable to self-administer intranasal intervention</td>
</tr>
<tr>
<td></td>
<td>• Unavailable for follow-up</td>
</tr>
<tr>
<td></td>
<td>• Unable to provide consent</td>
</tr>
</tbody>
</table>

3.3 Subject Protection and Confidentiality

We will seek study approval from the Yale Institutional Review Board (IRB) prior to study recruitment and enrollment. All study participants must sign written informed consent
forms prior to study enrollment. Consent forms will review the purpose, benefits, risks, and other pertinent information relevant to study investigation. Informed consent forms can be found in Appendix A of this document. Study participants will be given the opportunity to ask any questions and/or speak with study investigators prior to signing written informed consent paperwork. Study participation is voluntary and consent can be withdrawn at any time.

Before commencing the study, all relevant study personnel will undergo Health Insurance Portability and Accountability Act (HIPAA) training. All protected health information (PHI) will be obtained, stored, and accessed in compliance with HIPAA regulations. Once enrolled in the study, participants will be assigned and identified by a unique 5-digit code for data storage and analysis. All study data and information will be stored on university-approved encryption devices and only approved study personnel will have access to this information. Upon study conclusion, all PHI will be deleted in accordance with HIPAA policies. Study participants will be informed immediately of any events, problems, or changes which threaten their safety or confidentiality.

3.4 Recruitment

Study participants will be recruited from outpatient Yale Neurology clinics within the state of Connecticut. Following IRB approval, we will utilize Yale Neurology’s electronic medical records to perform chart review to screen for potential participants. The providers of appropriate candidates will be contacted and asked to inform their patients of the study. We will also encourage providers at Yale Neurology clinics to advertise the study to patients who might be suitable participants. We will advertise the study by posting recruitment flyers in provider workspaces and patient waiting areas.
Interested individuals will be provided with study contact information and undergo initial assessments, including MoCA and Hoehn & Yahr evaluations, to determine their eligibility based on the study’s inclusion and exclusion criteria. If eligible, individuals will receive informed written consent paperwork and be enrolled in the study if they choose to participate. This process will continue until a total of 250 participants are successfully enrolled.

3.5 Study Variables and Measures

The primary outcome in our study is mean change in olfaction performance from baseline to interventional conclusion at 8 weeks. To assess this measure, participants will be randomized to one of three interventions after enrollment: daily application of 40 I.U of intranasal insulin (Novolin-R), daily application of 80 I.U. of intranasal insulin (Novolin-R), or daily application of sterile intranasal saline. Participants will present to the study test site on the first day where the following baseline characteristics will be assessed and/or measured: age, gender, PD duration, Hoehn & Yahr score, anosmia/hyposmia duration, and PD subtype (tremor dominant, akinetic-rigid, or mixed type). Baseline olfaction performance, quantified by TDI score via use of Sniffin Sticks, will also be evaluated on the first day. All study participants will complete a baseline PDQ-39 questionnaire to assess their baseline quality of life.

On the first day, study participants will receive comprehensive training on the proper administration of their assigned intervention and will be educated on the signs and symptoms of hypoglycemia and how to handle any potential adverse effects. To continue participating in the study, participants must demonstrate their ability to administer the intervention using a test solution. Participants will then administer their first dose of their assigned intervention at
the study test center. For one hour after administration, study participants will be observed to
monitor for any adverse effects.

Participants must dispense their assigned intervention in one nostril, once daily, one hour
after taking their daily Parkinson’s medication. Participants must blow their nose prior to
administration, alternate the nostril used on a daily basis, and administer the intervention at
the same time every day. The intervention dosages will be packaged in unmarked Via Nase
devices which electronically atomize the interventions and enhance their delivery to the
brain\(^1\). Study pharmacists will package the interventions, ensuring that the Via Nase devices
for each intervention are identical and indistinguishable.

Study participants will then receive a 7-day supply of their assigned intranasal
intervention. To monitor for intervention adherence, participants will return to the study site
on a weekly basis to present their empty Via Nase devices and receive another 7-day supply
of the intervention. Additionally, participants will be provided with a log at study enrollment
to record any adverse effects. Participants will submit these logs on a weekly basis prior to
receiving additional doses.

3.6 Blinding of Intervention

Both study participants and investigators will be blinded to participation intervention
allocation. Participants will receive the same administration training and will follow the same
protocol for administration regardless of their intervention. Interventions will be prepared by
study pharmacists who will ensure all intranasal intervention delivery devices are identical.
Study pharmacists will be responsible for weekly intervention dispensing to maintain
intervention concealment. Outcome assessors will be unaware of study participant
assignment when assessing olfactory performance at baseline, intervention conclusion, and follow-up.

3.7 Assignment of Intervention

After enrollment, participants will be randomized to one of three interventions as explained above. The intervention allocation process will be conducted using simple randomization. A random number generator will assign participants to a number 1 through 3. Each number will correspond to a specific intervention group: number 1 will represent the control (intranasal saline) group, number 2 will represent the 40 I.U intranasal insulin group, and number 3 will represent the 80 I.U intranasal insulin group. With our large sample size of 250 total participants, this simple randomization approach will result in an approximately equal distribution of participants across the 3 interventions.

3.8 Data Collection

On the first day of the study, enrolled participants will present to the test site where we will assess their baseline characteristics including age, gender, PD duration, Hoehn & Yahr score, anosmia/hyposmia duration, and PD subtype. This information will be collected through a basic questionnaire and a brief clinical interview conducted by the study investigators. Additionally, we will measure baseline olfaction performance using Sniffin Sticks to obtain a composite TDI score. Baseline quality of life, quantified by total PDQ-39 questionnaire score, will be also be evaluated and recorded on the first day to assess for change in quality of life after intervention. All baseline assessments will be completed before participants receive the first dose of their assigned intervention.

For 8 weeks, participants will administer their assigned intervention once daily. Participants will visit the test site on a weekly basis to receive additional doses of their intranasal
intervention. To monitor adherence, participants must exchange their empty intranasal devices to receive new doses. Study personnel will hold conversations with participants if there is any evidence of missed doses or non-adherence.

Participants will undergo repeat olfaction performance testing and quality of life assessment at the intervention conclusion (8 weeks from treatment initiation). 16 weeks after enrollment, participants will return to the test site for a final round of olfaction performance testing and quality of life assessment to observe for any potential persistence of intervention effects. For additional information on the study timeline, please refer to section 3.11 (Timeline and Resources).

3.9 Sample Size Calculation

Using the Power and Precision 4 software, we derived a sample size of 250 total participants based on a two-tailed test with an alpha of 0.010, an effect size of 16.5%, a power of 80%, and a 20% loss to follow-up estimation. These calculations were based on studies whose primary outcome was change in olfactory performance as discussed in Chapter 2. We derived an effect size of 16.5% by averaging the relative effects, of 31% and 2.2%, from two studies which investigated the effects of intranasal insulin on olfaction performance in a non-PD study population\(^2\)\(^-\)\(^3\). Currently, there are no studies which have researched the effects of intranasal insulin on olfaction performance within a PD population. So, we used the relative effect sizes of 31% and 2.2% to estimate the effect our intervention might have within our population. As mentioned in Chapter 2, there is an increased risk of a type 1 error in our proposed study because our primary outcome will be measured at multiple times throughout the study duration. To negate this risk, we used the Bonferroni approach to calculate an alpha level of 0.010.
3.10 Data Analysis

The primary outcome in our study, mean baseline change in olfaction performance, will be assessed using repeated measures ANOVA based on per protocol and intention to treat analyses. Repeated measures ANOVA will be used to determine if there are statistically significant (p < 0.05) mean differences between the 2 intervention and control groups when olfaction performance is measured at baseline, intervention conclusion (8 weeks after treatment initiation), and follow up (16 weeks after treatment initiation; 8 weeks after intervention conclusion). Mean differences will be calculated for individual participants and intervention cohorts. The secondary outcome in our study, mean baseline change in quality of life, will also be assessed using repeated measures ANOVA.

The following characteristics will be assessed at baseline: age, gender, PD duration, anosmia/hyposmia duration, Hoehn& Yahr Score, and PD subtype (tremor dominant, akinetic-rigid, mixed). If randomization does not properly balance baseline characteristics across the intervention and control groups, linear regression will be used to perform multivariate analysis. The baseline characteristics will be analyzed using various statistical tests described in Table 2.

Table 2: Baseline Characteristics Statistical Analysis

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Description</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean age (years) ± SD</td>
<td>ANOVA</td>
</tr>
<tr>
<td>Gender</td>
<td>Female (number/total; %)</td>
<td>Chi-square</td>
</tr>
<tr>
<td></td>
<td>Male (number/total; %)</td>
<td></td>
</tr>
<tr>
<td>Parkinson’s Disease Duration</td>
<td>Mean time (years) ± SD</td>
<td>ANOVA</td>
</tr>
<tr>
<td>Anosmia/Hyposmia Duration</td>
<td>Mean time (years) ± SD</td>
<td>ANOVA</td>
</tr>
</tbody>
</table>
### Hoehn & Yahr Stage

<table>
<thead>
<tr>
<th>Parkinson’s Disease Subtype</th>
<th>Mean score ± SD</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor dominant: (Number/total; %)</td>
<td></td>
<td>Chi-square</td>
</tr>
<tr>
<td>Akinetic-rigid dominant: (Number/total; %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Type: (Number/total; %)</td>
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</table>

### 3.11 Timeline and Resources

Our proposed study will occur over a 24-month period once IRB approval is obtained. The first 6 months will be dedicated to advertisement, recruitment, staff training, facility arrangement, and miscellaneous coordination. The following 15 months will be used for rolling recruitment, participation enrollment, baseline testing, study commencement, and data collection. The final 3 months will be used for statistical analysis and final data collection for participants who enrolled late.

On the first day of the study, participants will present to the test site to meet with study investigators and personnel to obtain baseline testing and to receive the first dose of their assigned intervention. Participants will take their assigned intervention on a daily basis for a total of 8 weeks, with weekly follow ups scheduled for participants to receive additional doses and to address any adverse effect concerns. Participants will stop taking their intervention at 8 weeks and undergo repeat olfaction testing and quality of life assessment. Participants will return at 16 weeks for final olfaction testing and quality of life assessment. See Figure 1 for additional information.

Personnel required for the study will include a principal investigator, co-principal investigator, study pharmacists, study coordinators, research assistants, and study statisticians. These personnel will have various roles to ensure recruitment, consent, enrollment, baseline assessments, intervention allocation, intervention disbursement, data collection, and data analysis.
are completed within the study timeline. Additionally, one central office site will be required for the study duration.

**Figure 1: Study Timeline**

**Day 0:** Study commencement with baseline characteristics, baseline olfaction, and baseline quality of life assessment evaluated. First dose of intervention administered.

**Last day of Week 8:** End of intervention administration. Repeat olfaction performance and quality of life assessment evaluated.

**Last day of Week 16:** Final olfaction performance and quality of life assessment evaluated.
3.12 References


Chapter IV: Conclusion

4.1 Advantages and Disadvantages

Our proposed study on the use of intranasal insulin for olfaction dysfunction in PD patients offers several distinct advantages. Firstly, our study addresses the unmet need for a pharmacologic treatment option for olfaction dysfunction in PD. Several studies have investigated potential therapies for olfaction deficits secondary to PD, but results of these investigations have not supported use of these interventions in clinical practice. Additionally, many of these studies exploring potential interventions were limited as they utilized non-blinded study designs with small sample sizes. Our study aims to overcome these limitations by proposing a double-blind, randomized controlled trial with a sample size of 250 participants. With a double-blind protocol, both participants and outcome assessors will be unaware of intervention allocation which reduces the risk of bias influencing the results of our experimentation. Additionally, with a sample size of 250 participants, our study will have stronger external validity and more precise estimates of treatment effects.

Another advantage of our study is the secondary outcome measure of quality of life. The relationship between olfaction dysfunction and diminished quality of life has been recognized, but many previous studies did not assess their intervention’s impact on both olfaction and quality of life\textsuperscript{1,2}. Including quality of life assessment as a secondary outcome in our study is intended to provide a larger understanding of the potential benefits of our intervention. By doing so, we aim to provide a more meaningful assessment of the intervention’s effectiveness.

Despite the advantages, our proposed study has certain limitations. One limitation is the relatively short study duration and follow-up period. Our proposed protocol specifies that participants administer their intranasal intervention for 8 weeks with final follow up scheduled at
16 weeks (8 weeks after the last intervention dose). Since PD is a chronic and progressive condition, longer intervention administration and follow-up periods would be useful to assess the sustainability and long-term effects of the intervention. Another limitation of our study is our strict exclusion criteria. While these criteria were designed to minimize potential confounding and thus support a causal relationship between our intervention and outcome, our study sample may not reflect the full spectrum of PD patients. By excluding certain PD individuals with specific comorbidities or conditions, we reduce the external validity of our findings. Additionally, the strict exclusion criteria could lead to challenges in participant recruitment, potentially resulting in a smaller sample size or prolonger recruitment duration.

4.2 Clinical Significance

The clinical significance of our proposed study lies in its potential to address a prevalent and challenging symptom that significantly impacts patients’ quality of life\(^2\). Olfaction dysfunction is a common non-motor symptom in PD, often occurring early in the disease course, and persisting throughout disease progression\(^3\). The olfaction deficit in PD is accompanied by various psychological and social stressors for affected patients\(^4\). The lack of effective pharmacologic treatment for this specific symptom further adds to the challenges faced by these patients, as they have limited options to alleviate the olfactory dysfunction and associated decreased quality of life.

By investigating the efficacy of intranasal insulin on olfaction dysfunction in PD patients, our study aims to explore a novel and promising therapeutic approach. If successful, this intervention could improve olfactory function and subsequently enhance patients’ overall well-being and daily living experience. By focusing on a symptom that is often overlooked and
difficult to treat effectively, our study has the potential to address a critical aspect of PD symptom management.
4.3 References


Appendices

Appendix A: Compound Authorization and Consent Form

COMPOUND AUTHORIZATION AND CONSENT FORM FOR PARTICIPATION IN A RESEARCH STUDY

YALE SCHOOL OF MEDICINE

Study Title: Effect of Intranasal Insulin for Anosmia and Hyposmia in Parkinson’s Patients
Principal Investigator: Sara Schaefer, MD
Co-Investigator: Eden Anonye, PA-SII

Research Study Summary:
- We are asking you to join a research study.
- The purpose of this study is to investigate the efficacy of intranasal insulin for anosmia and hyposmia in Parkinson’s disease patients. Anosmia is a complete loss of the sense of smell. Hyposmia is a partial loss of the sense of smell.
- Study procedures will include: Once daily administration of intranasal placebo (intranasal saline) or intranasal insulin for 8 weeks. Participants will be randomly assigned to an intervention. Participants will receive a neurologic evaluation, baseline olfaction testing, and quality of life assessment on the first day. 2 follow-up visits are required for repeat olfaction testing and quality of life assessment.
- 3 total assessment visits are required. One on the first day of intervention administration, one at 8 weeks, and one at 16 weeks. Participants will present to the test site on a weekly basis to receive additional doses of their assigned intervention.
- These visits will take anywhere from 30 minutes to 3 hours.
- There are risks associated with this study. Potential risks include: hypoglycemia, nasal irritation, and/or breach of confidentiality.
- This study may or may not benefit you. If assigned to the intranasal insulin intervention, you may experience improved olfaction abilities and an improved quality of life. Regardless of your intervention assignment, results of this study will help to advance Parkinson’s disease research.
- There are other choices to you outside of this research. Please talk to your neurologist to discuss which options would be best for you.
- Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.
**Why is this study being offered to me?**
We are asking you to participate in this study because you have a 6-month history of anosmia or hyposmia secondary to idiopathic Parkinson’s Disease. We are looking for 250 participants to be part of this research.

**What is the study about?**
The purpose of this study is to investigate the efficacy of intranasal insulin in treating olfaction dysfunction secondary to Parkinson’s disease. Intranasal insulin is not FDA approved for treatment. However, intranasal insulin has shown promising results in other olfaction studies.

**What are you asking me to do and how long will it take?**
If you agree to take part in this study, we will review your medical records, you will receive a medical evaluation from a study neurologist, and you will complete a written test, called the Montreal Cognitive Assessment, to ensure you are eligible for the study.

If eligible for the study, you will undergo an initial olfactory performance test and complete a questionnaire to assess your perspective on the quality of your life. A computer program will randomly assign you to one of the following interventions: intranasal saline (placebo), 40 I.U. of intranasal insulin, or 80 I.U. of intranasal insulin. You will receive training from study personnel on how to properly administer the intranasal treatment.

You will take your assigned intranasal intervention once daily, one hour after taking your daily anti-Parkinson’s medication, for 8 weeks. You must alternate the nostril used on a daily basis and take the intranasal intervention at the same time every day. By agreeing to participate in this study, you agree not to take any other intranasal medications throughout the study duration.

You will receive a 7-day supply of your intranasal intervention at a time. You must return to the study test site after taking your intervention on the 7th day, and exchange all 7 of your empty intranasal devices, to receive another 7-day supply of your intranasal intervention. By agreeing to participate in this study, you agree to present to the test site on a weekly basis to receive additional intranasal intervention doses.

You will take your assigned intranasal intervention once daily for 8 weeks. After your final intranasal intervention dose during the 8th week, you will come to the study test site to complete repeat olfaction performance testing and complete another questionnaire to assess your perspective on the quality of your life. 8 weeks after your final intranasal intervention dose, you will come to the study test site to complete a final olfaction performance test and quality of life questionnaire.

**What are the risks and discomforts of participating?**
We do not anticipate any risks or discomforts while participating in this study. There is limited information on intranasal insulin use within Parkinson’s patients, but it has been well studied within the diabetic population and is well tolerated by most individuals. Common adverse effects include: nasal irritation, nose bleeds, sneezing, nasal discomfort, headaches, and dizziness. The most common adverse effect is nasal irritation.
Though unlikely, there is risk of loss of confidentiality. All associated medical personnel will be thoroughly trained on privacy protocols to minimize this risk.

**How will I know about new risks and/or important information about the study?**
We will inform all participants of any changes or updates that could influence their safety or willingness to participate in the study.

**How can the study possibly benefit me?**
You may experience improvements in your sense of smell and overall quality of life. These improvements are not guaranteed and you may not directly benefit from the study.

**How can the study possibly benefit others?**
The benefits to science and other people may include a better understanding of the utility of intranasal insulin in treating olfaction disorders in Parkinson’s disease. Results of this study will help to advance Parkinson’s disease research and may benefit future patients.

**Are there any costs to participate?**
If you take part in this study, you will not have to pay for any services, supplies, study procedures, or care that are provided for this research only (they are NOT part of your routine medical care). However, there may be additional costs to you. These include cost of transportation and your time to come to the study visits. You and/or your medical insurance must pay for services, supplies, procedures, and care outside of this study that are part of your routine medical care. You will be responsible for any co-payments required by your medical insurance.

**Will I be paid for participation?**
Participants who follow the study protocol as outlined above and present for all scheduled follow ups will receive a $100 Amazon gift card upon study conclusion.

**What are my choices if I decide not to take part in this study?**
Instead of participating in the study, you have some other choices. You could:
- Seek treatment without participating in the study. Please speak to your medical provider about other potential treatment options.
- Receive no treatment. Anosmia and hyposmia secondary to Parkinson’s disease are benign conditions that do not require treatment.

**How will you keep my data safe and private?**
We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to as required by US or State law.

All collected information will be kept confidential and comply with HIPAA regulations. Participants will be identified by a unique 5-digit code for data storage and data analysis. Physical data will be stored in locked cabinets and electronic data will be stored on encrypted software on password protected computers. Only designated study personnel will have access to
this information. All collected information will be destroyed in accordance to HIPAA policies upon study conclusion.

Results from the study may be published, presented at conferences, discussed with your neurologist, and/or shared with federal agencies including the U.S. Food and Drug Administration (FDA) and the U.S Department of Health and Human Services (DHHS). However, your name and personal health information will not be shared.

What information will you collect about me in the study?
The information we collect about you is called “Protected Health Information” (PHI). PHI is protected by federal law under the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). We cannot access, use, or share your health information without your permission.

Examples of the information we will access and use includes, but is not limited to:
- Yale New Haven Health medical records
- Information collected during study duration
  - Questionnaires
  - Physical exams
  - Research study records
  - Records about your study visits
  - Medical and laboratory results

What if I change my mind or no longer want to participate?
The authorization to use and disclose your health information collected in this study will never expire. Taking part in this study is your choice and you may withdraw at any time. No new information will be collected after you withdraw. Information collected prior to your withdraw date may still be used in study analysis.

You are still eligible to receive your standard medical care if you withdraw from the study. You will not lose access to your medical care or concede any legal rights or benefits. Withdrawing from the study will not change your relationship or the care you receive from your provider(s) or this institution.

Please inform study personnel if you wish to withdraw.

Who should I contact if I have questions?
Please feel free to ask any questions as they arise.

If you have study related questions, please contact the co-investigator at eden.anonye@yale.edu.
If you have questions or concerns about your rights as a study participant, please contact the Yale Institutional Review Board at hrpp@yale.edu

Additional information about this study will be published on https://www.clinicaltrials.gov/, as required by U.S. law.

Authorization and Permission?
Your signature below indicates that you understand and agree to the terms outlined in this document. Your signature indicates that you agree to participate in the study.

You will be provided with a copy of this form.

<table>
<thead>
<tr>
<th>Participant Printed Name</th>
<th>Participant Signature</th>
<th>Date</th>
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<tbody>
<tr>
<td>Person Obtaining Consent Printed Name</td>
<td>Person Obtaining Consent Signature</td>
<td>Date</td>
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</table>
Appendix B: Parkinson’s Disease Questionnaire (PDQ-39)

Parkinson’s Disease Questionnaire

Please complete the following by checking one box for each question.

Please consider the following when answering the questions: Due to having Parkinson’s disease, how often in the last month have you…

<table>
<thead>
<tr>
<th>Task</th>
<th>Never (0)</th>
<th>Occasionally (1)</th>
<th>Sometimes (2)</th>
<th>Often (3)</th>
<th>Always/unable (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had difficulty doing the leisure activities which you would like to do?</td>
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<tr>
<td>Had difficulty looking after your home, eg DIY, housework, cooking?</td>
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<td>Had difficulty carrying bags of shopping?</td>
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<td>Had problems walking half a mile?</td>
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<td>Had problems walking 100 yards?</td>
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<td>Had problems getting around the house as easily as you would like?</td>
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<td>Had difficulty getting around in public?</td>
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<td>Needed someone else to accompany you when you went out?</td>
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<td>Felt frightened or worried about falling over in public?</td>
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<td>Been confined to the house more than you would like?</td>
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<td>Had difficulty washing yourself?</td>
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<td>Had difficulty dressing yourself?</td>
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<td>Had problems doing up your shoe laces?</td>
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<td>Had problems writing clearly?</td>
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<td>Had difficulty cutting up your food?</td>
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<td>Had difficulty holding a drink without spilling it?</td>
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<tr>
<td>Felt depressed?</td>
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</tr>
<tr>
<td>Task</td>
<td>Never (0)</td>
<td>Occasionally (1)</td>
<td>Sometimes (2)</td>
<td>Often (3)</td>
<td>Always, unable (4)</td>
</tr>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>Felt isolated and lonely?</td>
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<tr>
<td>Felt weepy or tearful?</td>
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<tr>
<td>Felt angry or bitter?</td>
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<tr>
<td>Felt anxious?</td>
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<td>Felt worried about your future?</td>
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<tr>
<td>Felt you had to conceal your Parkinson’s from people?</td>
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<tr>
<td>Avoided situations which involve eating or drinking in public?</td>
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<tr>
<td>Felt embarrassed in public due to having Parkinson’s disease?</td>
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<tr>
<td>Felt worried by other people’s reactions to you?</td>
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<tr>
<td>Had problems with your close personal relationships?</td>
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<tr>
<td>Lacked support in the ways you needed from your spouse or partner?</td>
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<tr>
<td>Lacked support in the ways you need from your family or close friends</td>
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<tr>
<td>Unexpectedly fallen asleep during the day?</td>
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<td>Had problems with your concentration, eg, when reading or watching TV</td>
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<tr>
<td>Felt your memory was bad?</td>
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<tr>
<td>Had distressing dreams or hallucinations?</td>
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<td>Had difficulty with your speech?</td>
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<td>Felt unable to communicate with people properly?</td>
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<td>Felt ignored by people?</td>
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<td>Had painful muscle cramps or spasms?</td>
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<tr>
<td>Had aches and pains in your joints or body?</td>
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<tr>
<td>Felt unpleasantly hot or cold?</td>
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Total score:
## Appendix C: Montreal Cognitive Assessment (MoCA)

### MONTREAL COGNITIVE ASSESSMENT (MOCA)

**NAME:**

**Education:**

**Sex:**

**Date of birth:**

**DATE:**

<table>
<thead>
<tr>
<th>VISUOSPATIAL / EXECUTIVE</th>
<th>Points</th>
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<tr>
<td>Copy cube</td>
<td>5</td>
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<tr>
<td>Draw CLOCK (Ten past eleven) (3 points)</td>
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<table>
<thead>
<tr>
<th>NAMING</th>
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<tr>
<th>MEMORY</th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
<th><strong>No points</strong></th>
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<tbody>
<tr>
<td>Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.</td>
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<td>[ ]</td>
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<tr>
<td>1st trial</td>
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<tr>
<td>2nd trial</td>
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</thead>
<tbody>
<tr>
<td>Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order</td>
<td>[ ]</td>
<td>[ ]</td>
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<tr>
<td>Subject has to repeat them in the backward order</td>
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<tr>
<td>Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order</td>
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<tr>
<td>Subject has to repeat them in the backward order</td>
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<tbody>
<tr>
<td>Read list of digits (1 digit/sec.).</td>
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<tr>
<td>Subject has to repeat them in the forward order</td>
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<tr>
<td>Subject has to repeat them in the backward order</td>
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<tbody>
<tr>
<td>Repeat: I only know that John is the one to help today.</td>
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<tr>
<td>The cat always hid under the couch when dogs were in the room.</td>
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</table>

| FLUENCY / NAME maximum number of words in one minute that begin with the letter F | [ ] | [ ] | [ ] | [ ] | [ ] | [ ] |
| Fluency / Name maximum number of words in one minute that begin with the letter F | [ ] | [ ] | [ ] | [ ] | [ ] | [ ] |

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<tbody>
<tr>
<td>Similarity between e.g. banana - orange = fruit</td>
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<td>train – bicycle</td>
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<td>watch - ruler</td>
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<table>
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<tr>
<th>DELAYED RECALL</th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
<th>Points forUNCUED recall only</th>
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<tbody>
<tr>
<td>Has to recall words WITH NO CUE</td>
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<th>Date</th>
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<th>Year</th>
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<th>Place</th>
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Normal ≥ 26 / 30

TOTAL /30

Add 1 point if ≤ 12 yr edu
Appendix D: Sample Size Calculation

To account for 20% loss to follow up: $208 \times (1.2) = 250$ participants