THE ROLE OF THE NORADRENERGIC SYSTEM IN THE NONMOTOR SYMPTOMS OF PARKINSON'S DISEASE

A single center study exploring the association between orthostatic hypotension and the neuropsychiatric and neurocognitive features of Parkinson's disease

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List of Abbreviations

OH	Orthostatic Hypotension
NA	Noradrenergic
NP	Neuropsychiatric
PD	Parkinson's disease
AR	Adrenoceptor
ED	Erectile Dysfunction
HUT	Head Up Tilt
UPDRS	Unified Parkinson's Disease Rating Scale
H&Y	Hoehn & Yahr staging
LDED	Levodopa equivalent dose
OVS	orthostatic vital signs
AVP	arginine vasopressin
NE	norepinephrine
SCOPA-AUT	Scales For Outcomes In Parkinson's Disease - Autonomic Dysfunction
TOPF	Test of Premorbid Functioning
B-SIT	Brief Smell Identification Test
GDS	Geriatric Depression Scale
GAI	Geriatric Anxiety Inventory
FSS	Fatigue Severity Scale
AES	Apathy Evaluation Scale
AD-ACL	Activation-Deactivation Checklist to assess arousal
BRIEF-A	Behavior Rating Inventory of Executive Function, Adult
NPI-Q	Neuropsychiatric Inventory Questionnaire
VAS	Visual Analogue Score
CNS	Central nervous system
ANS	Autonomic nervous system
LC	Locus coeruleus

HR	Heart rate
BP	Blood pressure
DB	Deep breathing
BMI	Body mass index
FDA	Federal Drug Administration
GMP	Good Manufacturing Practice
IND	Investigational New Drug
C-SSRS	Columbia Suicide Severity Rating Scale
CBC	Complete Blood Count
CMP	Complete Metabolic Panel

Study Summary

Title	The role of the noradrenergic system in the nonmotor symptoms of Parkinson's disease
Short Title	NA in PD
Protocol Number	Velos: D19090 D-HH IRB: 31685
IND	*146199*
Phase	Phase 1 – Pilot
Methodology	Cross-sectional
Study Duration	12-24 months
Study Center(s)	Single-center: Dartmouth-Hitchcock Medical Center
Objectives	To explore the association between orthostatic hypotension (OH) and the neuropsychiatric (NP) and neurocognitive nonmotor features of Parkinson's disease (PD)
Number of Subjects	22 patients total (11 patients with PD and OH (PD+OH) and 11 PD patients without OH (PD-OH))
Diagnosis and Main Inclusion Criteria	Adults patients with a diagnosis of Parkinson's Disease with and without OH
Study Product, Dose, Route, Rationale	Yohimbine (5mg) is administered orally during Visit 2 in order to manipulate the noradrenergic system to determine the association between OH and NP symptoms in those with PD. Yohimbine is not administered as a treatment in this study, but as a pharmacologic tool to study the adrenergic system.
Statistical Methodology	In the primary analysis, between group (PD+OH and PD-OH) differences in nonmotor symptoms of fatigue, apathy, depression, anxiety, and neurocognition will be compared using nonparametric tests for ordinal variables.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Although Parkinson's disease (PD) is traditionally considered a movement disorder resulting from dopamine deficiency, there is increasing recognition that nonmotor symptoms are prevalent and drastically impact quality of life.[1-3] Orthostatic hypotension (OH) and symptoms of fatigue, depression, apathy, anxiety, and cognitive impairment (neuropsychiatric (NP) symptoms) are among the most bothersome symptoms in PD, and can occur early in the disease course.[1,3,4] OH in PD is due to a combination of cardiac sympathetic denervation, peripheral vascular sympathetic denervation, and baroreflex failure. [5-7] Involvement of central nervous system (CNS) areas that mediate autonomic nervous system (ANS) function, such as the anterior cingulate and insular cortex, have also been radiologically and pathologically associated with OH in patients with PD.[8, 9] Importantly, OH has been associated with depression, dementia, and poor prognosis in PD [5, 10-13], though not all studies agree[14] - likely due to methodological differences.[5]

The reasons for the association between OH and NP symptoms remains unknown.[5] A disease progression hypothesis suggests that as α-synuclein inclusions spread, brain areas that mediate OH and NP symptoms degenerate simultaneously.[15, 16] A neurochemical hypothesis suggests that since noradrenergic (NA) neurons are selectively damaged in PD, peripheral sympathetic degeneration is accompanied by degeneration of CNS NA areas such as the locus coeruleus (LC), which has been implicated in human cognition and arousal.[17-19] A third hypothesis is that OH itself leads to cognitive decline, since both OH-induced cerebral hypoperfusion and OH-associated supine hypertension can cause vascular brain injury,[20, 21] though at least one study refutes this theory. [22] Determining reasons for the association between OH and NP symptoms is critical since treatment will differ significantly: the neurochemical explanation suggests that norepinephrine (NE) replacement should treat OH simultaneously with NP symptoms, while the causal explanation suggests that treating OH will then lead to better cognition and mood. In addition, understanding the association between OH, NP symptoms, and NA dysfunction may help improve prognostication for patients with PD, and may help to identify a PD subgroup with distinct pathophysiology that requires a different treatment approach.[13] Unfortunately, studies to-date have not distinguished between these hypotheses.

In this study, we propose to test if NA dysfunction is associated with depression, cognition, apathy, anxiety, and fatigue in PD. First, we will test if OH in patients with PD is associated with other aspects of NP in which the adrenergic system plays a prominent role: fatigue/arousal,

attention/cognition, and apathy/depression. We will then conduct a series of physiologic tests to elucidate the contributions of central and peripheral NA dysfunction in OH in PD, and use these results to see if NA dysfunction mediates any associations between OH and NP symptoms.

These interrelated aims will help to determine if central NA dysfunction is associated with OH in PD, and whether NA dysfunction is associated with the NP symptoms in PD. These results may lead directly to treatment trials that target the NA system with the potential to significantly improve the lives of PD patients with bothersome nonmotor symptoms.

1.2 Investigational Agent

During study visit 2, a single-dose of yohimbine will be used to manipulate the NA axis and investigate central nervous system NA function (aims 2 and 3 - see below). Yohimbine has been used numerous times in a similar fashion in order to pharmacologically manipulate the α2-adrenoceptor (AR), as will be reviewed below.[32, 34-39] In this study yohimbine is not being tested for any clinical indication, but only for its unique pharmacologic actions; nevertheless, since yohimbine is not approved by the Food and Drug Administration (FDA), an investigational new drug (IND) application will be required. Yohimbine is chosen due to its unique antagonistic activity at the α2-ARs. Alternative drugs that are relatively specific for the α2-ARs, such as clonidine, are agonists that decrease overall adrenergic output. This can lead to potentially dangerous hypotension in individuals at risk and is therefore not an acceptable alternative to yohimbine.

Yohimbine (17α-hydroxyyohimban-16α-carboxylic acid methylester) (Fig. 1), an indole alkaloid found in a variety of botanical sources such as the Rauwolfia root, is the principal alkaloid extracted from the bark of the Pausinystalia yohimbe tree.[23] It has also been called quebrachine, aphrodine, corynine, and hydroaerogotocin. Yohimbine is a potent selective α2-(AR) antagonist with weaker α1-antagonist activity, as demonstrated by radioreceptor ligand binding assays and by pharmacological studies.[24] The predominant use of yohimbine has been as a pharmacological tool to study the involvement of α2-ARs in the regulation of autonomic function, and for the treatment of impotence in males. As will be detailed below, yohimbine has a long history of safe use in clinical medicine and in clinical trials, including numerous recent studies.[25-32] It is not currently commercially available in the United States as a drug, but it is widely distributed as a dietary supplement even though these supplements often contain pharmaceutical grades of yohimbine.[33] Yohimbine is still available in several other countries including Canada.

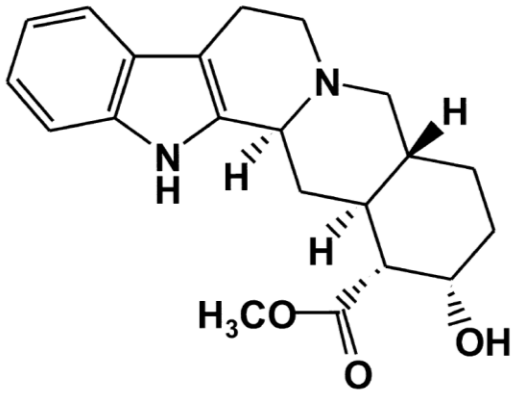


Figure 1 - YOH chemical structure

1.3 Preclinical Data

Yohimbine is a nonspecific α2 NA antagonist. Its downstream effects are complex and include increasing sympathetic activity on blood vessels by way of negative feedback.[23] In addition to its long track records in human studies, it has been used to manipulate the noradrenergic system in animals for decades.[40]

Pertinent to this clinical investigation, yohimbine has been used to study animal models of stress, depression, cognition, arousal and pupillary function. Wang and colleagues used yohimbine to study the central release of norepinephrine from the locus coeruleus in a rat model of stress-induced depression.[41] Koss reviewed central α2 ARs in rats and cats and used yohimbine and clonidine, an α2 agonist, to study pupillary dynamics.[42] Berridge et al. also studied pupillary dynamics using yohimbine in rats.[43] Coull [44] and Arnsten et. al.[45] reviewed the role of norepinephrine and α2-ARs in attentional and arousal aspects of cognition in animals. Verwaerde et al. tested yohimbine in a dog-model of neurogenic OH and found that yohimbine improved sympathetic tone and OH.[46]

1.4 Clinical Data to Date

Over the last few decades, yohimbine has been used in hundreds of clinical trials around the world. In this clinical investigation, we will use yohimbine to manipulate the adrenergic system and not for a particular clinical indication. However, in order to focus on safety and its effects on the adrenergic system, we will review prior yohimbine studies that focused on the main subjects of the current investigation: pupillary pathways, neuropsychiatric symptoms, and PD and related disorders. We will also briefly review clinical trials of yohimbine for erectile dysfunction (ED), which is the most frequent indication, in order to illustrate yohimbine's safety record.

Pupillary dynamics

Phillips et al. administered yohimbine in human subjects to investigate the role of central α2 AR receptors and pathways in pupillary dilation and constriction.[35] They used a 22 mg dose, while we plan to use a 5 mg dose in case some of our patients with autonomic dysfunction have adrenergic denervation hypersensitivity[47, 48] and have an exaggerated sympathomimetic effect. These authors found that yohimbine has a sympathomimetic effect on the pupils, most prominent in lighted conditions, concluding that it acts on central NA pathways. No adverse events were reported, but neither was any safety data. While prior studies have looked at pupillary changes in Parkinson's patients, [49] we are not aware of the use of yohimbine to study the NA pupillary system in this population.

Neuropsychiatric and neurocognitive clinical data

Halliday has shown that yohimbine can speed human processing time, likely through increasing norepinephrine.[31, 50, 51] Yohimbine 21.6 mg has also been shown to increase anxiety and cocaine craving in cocaine abusers, but not healthy controls.[29] High-dose (0.4 mg/kg) intravenous

yohimbine has been shown to increase impulsivity and blood pressure in 23 healthy controls, with no adverse events reported.[31] A recent randomized clinical trial in 40 adults showed that yohimbine 10.8 mg is well-tolerated and may be useful to augment exposure therapy for social anxiety disorder.[25] Another randomized controlled trial showed that 10 mg of yohimbine increases norepinephrine levels but does not augment exposure therapy for fear of flying in 67 adults, and again the treatment was safe.[27] A similar trial targeting specific phobias in 56 individuals found that yohimbine 15 mg did not augment therapy but was safe.[52] We are not aware of a study using yohimbine to study the role of the NA system in PD, as we propose to do.

Erectile dysfunction

Yohimbine has been widely used for erectile dysfunction (ED) and was one of the most widely prescribed agents prior to the age of sildenafil (Viagra) and other phosphodiesterase inhibitors. Vogt et al. tested over 80 patients in a double-blind trial using yohimbine at 30 mg per day for 8 week for ED and found it to be well-tolerated with only few mild side effects.[43] Lebret and colleagues also tested yohimbine for ED in 45 patients and again found it safe (and effective).[53] The use of yohimbine for ED was recently reviewed.[54, 55] Aggregated evidence suggests that yohimbine is safe, and serious adverse events are infrequent and reversible.

Parkinson's disease and orthostatic hypotension

Senard and colleagues tested whether yohimbine 2 mg three times daily of yohimbine was effective in treating orthostatic hypotension in individuals with PD.[56] They found no effect on blood pressure, but yohimbine was deemed to be safe in individuals with PD. Onrot and colleagues tested yohimbine 5 mg daily to treat low blood pressure in patients with autonomic failure, and they found it to be effective and well-tolerated.[38] Yohimbine has also been found to increase blood pressure in normal volunteers.[48] Richard and colleagues tested yohimbine in Parkinson's patients with a history of anxiety, depression, and panic attacks and found that yohimbine could induce panic or anxiety in susceptible individuals.[57] No patients without a history of anxiety or panic attacks experienced panic with yohimbine, even at high doses of 21.6 mg. As a result of this study and others, we will exclude patients with a history of panic attacks and warn subjects about this potential adverse event during consent. Petrie et al. tested yohimbine 0.65 mg/kg (a much larger dose than we plan to use) in a non-Parkinsonian population, including elderly individuals, to monitor the effects on plasma norepinephrine and found that yohimbine increases catecholamines.[39]

Pharmacokinetics

Single-dose pharmacokinetics studies using yohimbine HCL demonstrated that yohimbine is rapidly absorbed and eliminated (both mean Tmax and elimination $T1/2 < 1$ hr).[23] The average absorption half-life is 0.17 ± 0.11 hr, and absorption of yohimbine from the gut is generally complete in 45–60 min.[23, 58] To ensure safety, our patients will be observed for at least 3 hours after yohimbine administration or until any adverse effects experienced during the visit are

completely resolved and blood pressure and heart rate have returned to the pre-yohimbine baseline.

1.5 Dose Rationale

Oral and intravenous doses of between 5 mg and 30 mg have been used in prior clinical trials using yohimbine to manipulate the NA axis in human (see Section 1.4 Clinical Data to Date). Since patients with PD are prone to sympathetic degenerative neuropathies, [59] with accompanying sympathetic denervation hypersensitivity, [60, 61] we will be administering a low dose of 6 mg of oral yohimbine - similar to prior studies demonstrating safety in this population.[62, 63, 64]

1.6 Risk/Benefits

Overall risks of this protocol are minimal. All risks will be spelled out in simple language on the consent form. All subjects must give informed consent prior to research participation.

The surveys and interviews are non-invasive and minimal risk. There is a possibility that some questions might be embarrassing or uncomfortable. Patients will be reminded that they have the right to refuse to answer any questions they wish.

With research participation, there is always a risk of data and privacy breach. All measures will be taken to protect the confidentiality of patients involved in the study by assigning a study identifier to each subject. Study data will be stored on a secure, web-based application called REDCap, and/or on a Department of Neurology computer or server managed by the Information Services department at Dartmouth-Hitchcock Medical Center. Paper records will be kept in Department of Neurology research offices, which are locked when not in use, and in long term storage managed by the Records Management/Health Information Services department. Ten years after completion of the study, all identifying information will be eliminated.

Pupillometry, vibrotactile detection thresholds, and neurocognitive/neuropsychiatric tests are non-invasive and carry minimal risk. Cognitive questionnaires could conceivably be frustrating to the patient, or questionnaires may ask about troubling symptoms such as depression. Patients will be reminded they can withdraw at any time or choose not to answer certain questions they find bothersome.

Venipuncture will be required to obtain blood samples as part of our protocol. Venipuncture is minimal risk but carries with it the risk of discomfort, bruising, bleeding, swelling, infection, and pain. Standard precautions will be followed during intravenous catheter placement and blood draws by trained personnel accustomed to these procedures as part of tilt-table testing.

Both autonomic testing and tilt-table testing are minimally invasive but can precipitate hypotension, bradycardia or tachycardia, palpitations, anxiety, presyncope, or frank syncope with

accompanying cardiac arrhythmias. A study neurologist will be readily available during all autonomic tests, and a cardiac electrophysiologist and cardiac nurse will be physically present during all tilt-table tests. The protocol procedures will be stopped or paused for bothersome or worrisome symptoms. In the unlikely event of a dangerous arrhythmia or dangerous hypotension during the tilt-table test, the cardiologist will stop the test and administer the appropriate treatment. Known cardiac disease is a study exclusion criteria, to further minimize any potential risk.

We will administer yohimbine as part of this protocol. Possible side effects of yohimbine may include, but are not limited to, hypertension, tachycardia, increased motor activity, irritability, anxiety, insomnia, tremor, increased chance of erection, dizziness, nausea, headache, and skin flushing. This medication has a long record of safety and use throughout the world, as reviewed above, so we do not anticipate any barrier to its use in this study. Prior research has documented its safety in PD and syncope.[65, 66]

Subjects will be observed by research personnel while on yohimbine until the effects of the medication wear off.

For participation in this study, participants will need to hold adrenergic medications for at least three half-lives and dopaminergic medications on the morning of the test.

Holding levodopa and other dopaminergic medications for a morning presents minimal risk. This is not dangerous but may make subjects feel stiffer or more uncomfortable than normal. All subjects will agree to this as part of the informed consent process. This is not an uncommon practice for various clinical procedures such as deep brain stimulation evaluation so should not pose a problem.

Subjects may have to wean off or hold medications that interfere with autonomic testing. This will be done with the guidance of their primary neurologists, with potential risks spelled out prior to patients agreeing to participate in this study. Subjects will only be enrolled if their primary neurologist feels that holding a medicine would represent minimal risk. Examples of medications that affect the noradrenergic axis and would have to be held for at least three half-lives include pyridostigmine, midodrine, stimulants (e.g. methylphenidate), venlafaxine, or droxidopa. Holding these medications could cause sleepiness, mild hypotension, increase appetite, anxiety, agitation, abnormal sweating, or other potentially bothersome symptoms, so their primary neurologists would need to approve participation when these medications are taken daily and need to be held.

Subjects will also hold food and coffee the morning of their tilt-table test, which might present a nuisance but not any significance risk since we are excluding patients with diabetes.

2 Study Objectives

Primary Objective is to explore the association between orthostatic hypotension (OH) and several neuropsychiatric and neurocognitive nonmotor features of Parkinson's disease (PD).

Secondary objectives include the following:

- To explore the association between central noradrenergic dysfunction, OH, and nonmotor symptoms of PD by measuring hormonal response to head up tilt-table (HUT) testing before and after administration of yohimbine
- To explore the association between central noradrenergic dysfunction, OH, and nonmotor symptoms of PD by measuring pupillometric parameters before and after administration of yohimbine

3 Study Design

3.1 General Design

This is a cross-sectional pilot study comparing 11 PD patients with OH to 11 PD patients without OH. OH will be defined as a drop in systolic BP of ≥ 20 mmHg or diastolic BP ≥ 10 mmHg within 5 minutes of standing (measured at 1, 2, and 5 minutes).[59, 67] The study will include two clinical visits and a follow-up phone call 24-72 hours after the 2nd visit. Visits will last approximately 4-5 hours each. After consent has been signed, data from prior neurological exams, such as the H&Y staging, orthostatic vital signs (OVS) and UPDRS scores will be collected from a subject's medical record as part of study data.

For visit 1, subjects will be required to hold levodopa and other dopaminergic PD drugs on the morning of the visit, and other adrenergic medications for at least three half-lives. Subjects will bring their AM dopaminergic doses to be taken at the visit at the direction of study staff in order to coincide with the timing of procedures. Visit 1 will consist of reviewing informed consent and inclusion/exclusion criteria. The PI will confirm eligibility, (women of childbearing potential will undergo a serum pregnancy test as part of this eligibility review). Demographics, medical history, history and current use of alcohol, current and prior smoking status, and concomitant medications will be recorded. HR and BP response to deep breathing (DB) and Valsalva maneuvers, and vibrotactile detection thresholds, will also be tested. The subject will also undergo neurocognitive testing and neuropsychiatric assessments. OVS will be taken before administration of the subject's dopaminergic medications, and at approximately 30 minutes and 1 hour after dopamine administration. Dynamic pupillometry will be evaluated before and approximately 1 hour after administration of the subject's dopaminergic medications. If the subject has not had a CBC and CMP in the past 6 months, the PI will order and review these blood levels for any clinically significant abnormalities. This visit will last approximately 4-5 hours.

For Visit 2, subjects will again be required to hold levodopa and other medications that may interfere with autonomic testing. Women of childbearing potential will have a urine pregnancy test performed prior to the HUT. An IV will be placed as per HUT procedure. HUT testing will be conducted twice, once prior to and once after yohimbine administration. The subjects will complete visual analogue sales measuring anxiety, mood, and fatigue prior to and after yohimbine administration. Dynamic pupillometry will also be evaluated prior to yohimbine administration and after yohimbine administration. Serum arginine vasopressin (AVP) and norepinephrine (NE) will be drawn twice prior to yohimbine administration and twice after yohimbine administration. One draw will be in the supine position, and the other will be during the head up tilt as outlined below, and then these two draws will be repeated after yohimbine (see Section 7.3, Figure 2).

A follow up study phone call will be made by the study coordinator 24-72 hours after study visit 2. Any adverse events which may have occurred since the study visit will be captured on the subject's AE log.

3.2 Primary Study Endpoints

The primary study endpoint will be between the group (OH verses non-OH) difference in fatigue (measured with the self-reported FSS), depression (measured with the self-reported GDS), apathy (measured with the AES and NPI-Q), anxiety (measured with the GAI and NPI-Q), and cognitive impairment (measured as an average composite z-score on the neurocognitive battery).

3.3 Secondary Study Endpoints

Secondary study endpoints will be:

- Difference between OH and non-OH group in change in supine and orthostatic catecholamine and AVP levels before and after yohimbine administration
- Difference between OH and non-OH group in change in time to pupillary redilation before and after yohimbine
- Change in self-reported anxiety, mood and fatigue before and after yohimbine
- Between group difference in baseline BP rise with yohimbine administration
- Difference in time to recovery of BP after 60 degree HUT before and after yohimbine administration
- Correlation between sympathetic function (measured with pupillary redilation and beat-to-beat BP) and levodopa use

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Participant able to provide informed consent
2. Diagnosis of Parkinson's disease confirmed by a DH neurologist according to Movement Disorder Society criteria, with the exception that "Red flag" 5a will not be used (severe autonomic failure within five years of disease onset).[68]
3. All subjects must have CMP and CBC drawn within 6 months of study visit 1, with results in the normal range or with abnormal results not considered to be clinically significant in the investigator's opinion. If CMP, CBC have not been drawn within 6 months of study enrollment, they will be ordered, drawn and reviewed for abnormalities of clinical significance as part of the screening process.
4. Female patients must be post-menopausal (at least one year) or have undergone surgical sterilization or hysterectomy at least 3 months before Visit 1. Women of childbearing potential must not be breastfeeding, have a negative pregnancy test at study entry and prior to yohimbine administration, have no intention to become pregnant during the course of study participation, and use contraceptive drugs or devices for the two weeks prior to and after yohimbine administration. Male patients with partners of child-bearing potential, must agree to use adequate contraception for 2 weeks before and after yohimbine administration. Adequate contraception includes oral, transdermal, or injectable (depot) estrogen and/or progestogen, selective estrogen receptor modulator therapy, intrauterine contraceptive device, double barrier method (e.g., condom and diaphragm or spermicidal gel) or vasectomy.

4.2 Exclusion Criteria

1. Diagnosis or previous history of diabetes of any kind
2. Known autonomic neuropathy unrelated to PD
3. History of or current cardiac, liver or renal disease that, in the opinion of the investigator, may put the patient at risk because of participation in the study
4. Known condition that in the investigator's opinion would be a contraindication to HUT testing or yohimbine challenge (e.g. decompensated cardiac disease, severe positional vertigo; severe anxiety, known panic disorder[69])
5. Current use of catecholaminergic medications (e.g. stimulants, droxidopa, midodrine) that cannot be held for at least three half-lives
6. Inability to hold PD medications for at least 12 hours
7. History of major depressive or bipolar disorder preceding the diagnosis of PD,[69] or diagnosis or previous history of psychiatric illness that in the investigator's opinion would affect the subject's ability to successfully participate in the study.

8. Any history (other than PD) that could affect neurocognitive function, such as history of traumatic brain injury (head injury with loss of consciousness > 1 hour), known dementia unrelated to Parkinson's or related diseases; developmental delay, multiple sclerosis, epilepsy, intellectual deficit, diagnosed and untreated sleep apnea; untreated syphilis; HIV; or other conditions that, based on the investigators opinion, could interfere with neurocognitive evaluation.
9. Known ophthalmologic disease such as untreated cataract, glaucoma, optic neuritis, orbital trauma, or other neuroretinal disease that might impact pupillary function
10. Severe illness within 30 days prior to enrollment.
11. Use of opiate, procholinergic, or other medications influencing pupillary function that cannot be held for three half-lives
12. In the Investigator's opinion, subject would be unable to successfully participate in the study for any reason.

4.3 Subject Recruitment and Screening

Participation in this research requires informed consent according to Institutional Review Board (IRB) guidelines. A signed IRB approved Consent Form is the means of documenting this understanding. Subjects must be able to consent for themselves to be able to participate in this study and have received an exact copy (at point of signature acquisition). Potential recruits are instructed that their participation is voluntary and that their medical care will not be altered in any way should they elect not to participate.

Initial recruitment will take place during routine clinic visits with a DH neurologist caring for patients with PD. The study will be briefly described to the patient. If the patient is interested, a study coordinator will contact them to explain the study in detail and confirm eligibility. Interested subjects will then be sent informed consent information (i.e. study procedure, risks, and benefits) to review at home, and they will have the opportunity to ask questions prior to scheduling the first study visit. Completion of the informed consent process will then take place face-to-face at the onset of Study Visit 1, prior to any data collection. Data regarding the subject's UPDRS, H&Y standing and OVS will be gathered from the subject's medical record after consent has been obtained. All study visits and procedures will take place at Dartmouth-Hitchcock Medical Center, Lebanon, NH.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

A subject may be withdrawn from the study prior to the expected completion of that subject for safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, or subject is lost to follow up. Subjects will be deemed lost to follow up after a minimum of 3 documented phone calls, emails, or certified letters of a physician or designee at the study site to

the subject or emergency contact. If a participant is deemed lost to follow up, the PI or designee will mail a signed letter to the patient to inform them of their withdrawal from the study.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

All study procedures will be discontinued for the subject at the point of being classified as "Withdrawn." Data collected up to the point of subject withdrawal may be used for analysis. If a patient is terminated early from the study as a result of an adverse event related to study procedures, every effort will be made to follow the patient until the adverse event resolves.

5 Study Drug

5.1 Description

Yohimbine is a potent selective α2-adrenoceptor (AR) antagonist with weaker α1-antagonist activity.

5.2 Administration Regimen

One yohimbine tablet (5mg) will be dispensed to the subject and administered orally at Visit 2.

5.3 Preparation and Administration of Study Drug

Yohimbine will be produced in a GMP compliant facility by **CHEPLAPHARM ARZNEIMITTEL GMBH** (ZIEGELHOF 24 GREIFSWALD 17489 GERMANY). The appropriate dose will be dispensed by the Investigational Pharmacy at Dartmouth-Hitchcock Medical Center and administered to the subject by a licensed clinician during Visit 2.

5.4 Subject Compliance Monitoring

Subjects will be asked to hold dopaminergic medications on the morning of Visits 1 and 2 and adrenergic medications for at least three half-lives on the mornings of Visit 1 and 2. If subjects do not comply with this, the visit will be rescheduled.

5.5 Prior and Concomitant Therapy

As part of each study visit, concomitant medications will be recorded and then reviewed. Subjects will be asked to hold levodopa and other dopaminergic medications for the morning of Visits 1 and 2. In addition, subjects may have to wean off or hold medications that interfere with autonomic testing and pupillary testing for Visits 1 and 2. Examples of medications that affect the NA axis and would have to be held for at least three half-lives include pyridostigmine, midodrine, stimulants (e.g. methylphenidate), venlafaxine, or droxidopa. This will be done with the guidance of their primary neurologists, with potential risks explained prior to patients agreeing to participate in this study. Subjects will only be enrolled if their primary neurologist feels that holding a medicine would represent minimal risk.

5.6 Packaging

Yohimbine preparation will be conducted in a GMP facility, **CHEPLAPHARM ARZNEIMITTEL GMBH**. Each package containing yohimbine will be pre-numbered with a lot number by the manufacturer prior to shipment and delivery to DHMC. The yohimbine hydrochloride tablets will be shipped to the Dartmouth-Hitchcock Investigational Pharmacy as 50 or 100 tablets in platelets (PVC / Aluminum) of 10 tablets

5.6.1 Receipt of Drug Supplies

Yohimbine will be shipped directly from **CHEPLAPHARM ARZNEIMITTEL GMBH** (ZIEGELHOF 24 GREIFSWALD 17489 GERMANY) to the Investigational Pharmacy at Dartmouth-Hitchcock Medical Center. Upon receipt of the study treatment supplies by the receiving pharmacy, the designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files.

5.6.2 Storage

Yohimbine will be stored at the Investigational Pharmacy at Dartmouth-Hitchcock Medical Center in a dry, cool location.

5.6.3 Dispensing of Study Drug

The yohimbine tablet will be dispensed at Visit 2. The Dartmouth-Hitchcock Investigational Pharmacy will keep record of all study drug issued. Notation will also be made in the participants' electronic medical records regarding the dispensation of the study drug

5.6.4 Return or Destruction of Study Drug

At the completion of the trial, a final reconciliation of study drug shipped, consumed, and remaining will be performed. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused study drug. All drug remaining at the completion of the study will destroyed on site and will be documented in the study files.

6 Study Devices

6.1 Description of NeurOptics® PLR-3000

All subjects will undergo pupillometric evaluation with the NeurOptics® PLR-3000. The PLR-3000 system automatically measures monocular resting pupillary size using infrared light in a dark room, and then uses a brief light flash to measure minimum post-contraction pupillary size, contraction velocity, contraction latency, redilation velocity, and time of pupillary redilation. Pupillometric methods have been described previously [70-72] and will modified for use with the NeurOptics system. Testing will be done twice in each eye. Binocular pupillometric data collection will take less than 5 minutes to obtain. Bilateral results will be averaged for final

comparison. If there is a unilateral preexisting condition (e.g. untreated cataract), pupillometric evaluation will be limited to the unimpaired side with no averaging. We will measure these parameters at baseline with the patient at rest and room lights as dim as possible, then again with lights on. Pupillometry will be performed in the same room to maintain minimal variation in luminance. We will repeat these studies after yohimbine administration at the time of the second HUT.

7 Study Procedures

7.1 Schedule of Assessments

Event/Assessment	Visit 1			Visit 2 (occurs no more than 30 days after V1)		Follow-Up Phone Call (24-72 hours after Visit 2)
Informed consent	X					
Inclusion/Exclusion criteria	X					
Demographics	X					
Medical history	X					
History and current use of alcohol	X					
Current and prior smoking status	X					
UPDRS, Hoehn & Yahr staging	X					
Orthostatic vital signs (OVS)	X Baseline: holding L-dopa	X 30 min after L-dopa administration	X 1 hour after L-dopa administration	X pre yohimbine administration	X post yohimbine administration	
Serum Pregnancy Test (WOCBPO)[i]	X					

Event/Assessment	**Visit 1**			**Visit 2**		**Follow-Up Phone Call (12 to 72 hours after Visit 2)**
Urine Pregnancy Test (WOCBPO)				X		
Concomitant medications	X			X		X
Adverse Events	X			X		X
SCOPA-AUT	X					
HR and BP response to DB and Valsalva	X					
Vibrotactile detection thresholds	X					
Neurocognitive testing	X					
Neuropsychiatric assessment	X					
Neuropsychiatric assessment (Informant)	X					
Dynamic pupillometry	X (holding levodopa)		X (1 hour after levodopa administration)	X (pre yohimbine administration)	X (post yohimbine administration)	
C-SSRS Baseline Version	X					

Event/Assessment	**Visit 1**		**Visit 2**		**Follow-Up Phone Call (12 to 72 hours after Visit 2)**
CSSRS- Since Last Visit Version			X		
IV placement			X		
HUT			X (pre yohimbine administration)	X (post yohimbine administration)	
Visual analogue scales measuring anxiety, mood, fatigue			X pre -yohimbine administration	X post- yohimbine administration	
Serum AVP [ii] and NE [iii]			X Pre Yohimbine administration	X Post Yohimbine administration	
Safety Labs (CBC, CMP)[iv]	X				

[i] Women of Child Bearing Potential Only
[ii] AVP will be draw after approximately 30 minutes supine and again at approximately 15 minutes upright tilt to 60 degrees.
[iii] NE drawn after approx.30 minutes supine and again at approximately 5 minutes after upright tilt to 60 degrees
[iv] If labs have been drawn within past 6 months and are WNL or with abnormalities that are NCS; those can be utilized for inclusion

7.2 Visit 1

- Informed consent
- Confirmation of Inclusion/Exclusion
- Demographic collection
- Medical History data collection
- Vital Signs
- Serum Pregnancy Test (women of childbearing potential only)
- Serum Safety Labs for CBC, CMP (if not completed in past 6 months)
- Orthostatic Vital Signs
    - Baseline, (holding AM dopamine)
    - Approx 30 minutes after dopamine administration
    - Approx 1 hour after dopamine administration
- Peripheral Nerve Testing
    - HR and BP response to DB and Valsalva
    - Vibrotactile detection thresholds
    - SCOPA-AUT survey
- Dynamic Pupillometry
    - Prior to dopamine administration
    - Approximately 60 minutes post-dopamine administration
- Neuropsychiatric and neurocognitive testing (approx. 1.5 hours in length)
- Columbia Suicide Severity Rating Scale, (Baseline)

Patients will be informed to hold dopaminergic medications on the morning of Visit 1 and adrenergic medications for at least three half-lives. After providing informed consent and meeting inclusion/exclusion criteria, subjects will be asked to complete a structured interview using a standardized questionnaire/data abstraction form to obtain demographic and clinical data. Information that the patient does not know will be obtained from the medical record and the patient's primary neurologist and entered into the standardized questionnaire/data abstraction form.

The following demographics and disease characteristics will be captured:

- Age, sex, race and ethnicity
- Income
- BMI
- Highest level of education completed
- H&Y staging
- Concomitant medications including levodopa and LDED

- Years since PD diagnosis
- Comorbidities (Charleston Comorbidity Index)
- Current and prior alcohol use
- Current and prior smoking status.

Subjects will also have their OVS done at baseline (holding AM dopamine) and then again at approximately 30 minutes and 1 hour after dopamine administration.

Neuropsychiatric and neurocognitive testing

Patients will complete on one occasion a battery of neurocognitive measures.
This will include:

- The Test of Premorbid Functioning (TOPF) , a word reading based estimate of premorbid IQ [74]
- Montreal Cognitive Assessment (MoCA) [70]
- Brief University of Pennsylvania Smell Identification Test (B-SIT) [75]
- Digit Span subtest from the Wechsler Adult Intelligence Scale – IV [76]
- Symbol Digit Modalities Test (Smith, 1968) [77]
- Trail Making Test [78]
- California Verbal Learning Test – II [79]
- Rey Complex Figure Test [80]
- DKEFS Color-Word Interference Test [81]
- Phonemic and Semantic Verbal Fluency [82]
- Behavior Rating Inventory of Executive Function – Adult [83]

Patient neuropsychiatric characteristics will be assessed by having them complete on one occasion:

- The Geriatric Depression Scale (GDS) [84, 85]
- Geriatric Anxiety Inventory (GAI) [86, 87]
- Fatigue Severity Scale (FSS) [88]
- Apathy Evaluation Scale (AES) [89, 90]
- Activation-Deactivation Checklist to assess arousal (AD-ACL) [91]

Patients will also complete a visual analogue scale before and after yohimbine to assess for acute changes in symptoms such as anxiety, fatigue, and concentration/attention [VAS; score ranging from 0% (no symptoms) to 100% (most severe symptom possible)]. [95]
An informant (when available) will complete informant report versions of the BRIEF-A, AES, as well as the Neuropsychiatric Inventory Questionnaire (NPI-Q). [92]

The total time for neurocognitive and neuropsychiatric testing will be approximately 1.5 hours.

Peripheral nerve testing:

This following peripheral nerve testing will performed by trained autonomic technicians and interpreted by the PI or a sub-I.

- HR and continuous BP variability monitoring with deep breathing and Valsalva.
- Patients will answer a validated survey to quantify their autonomic symptoms (the SCOPA-AUT).[93]
- Measurement of vibrotactile detection thresholds.[94]
- Dynamic pupillometry testing prior to subjects taking their levodopa-, and then again approximately 60 minutes after ingestion. See section 6.1 for pupillometry protocol.

7.3 Visit 2

HUT will be done first thing in the morning, since subjects will be holding their levodopa and other medications that could interfere with autonomic testing. Subjects will fast and abstain from coffee the morning of testing but will be encouraged to hydrate exuberantly.

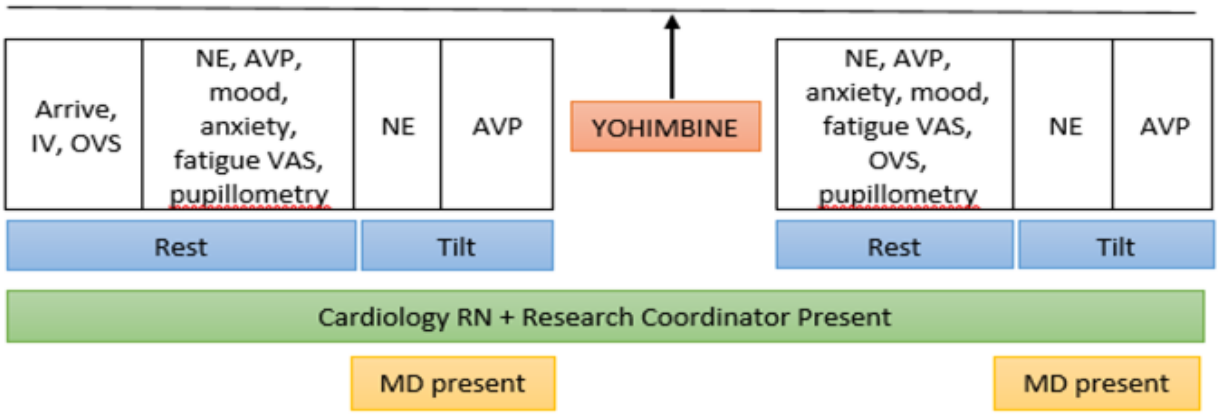
Prior to beginning the HUT, the following will occur:

- Collection of adverse events since consent was signed /changes in medical history
- Collection of changes in concomitant medication will be collected.
- A C-SSRS, (Since Last Visit), will be also be performed.
- Urine pregnancy test will be performed prior to starting the HUT, (if a women is of childbearing potential,).

The following procedures will be performed as part of the HUT and measured per HUT protocol [6, 22,] while under the supervision of a cardiac electrophysiologist, cardiology nurse and study coordinator.

- IV will be placed per standard HUT procedure.
- After approximately 30 minutes of supine rest:
    - Serum AVP and NE levels draw for baseline level
    - VAS scale completion for baseline/resting anxiety, fatigue and mood, ([VAS; score ranging from 0% (no symptoms) to 100% (most severe symptom possible)][95).]
- Pupillometric evaluations (see Figure 2).
- Tilt table to approximately 60 degrees for approximately 15 minutes; return to supine
- Yohimbine administration
- VAS scale completion for baseline/resting anxiety, fatigue and mood, ([VAS; score ranging from 0% (no symptoms) to 100% (most severe symptom possible)][95).]
- Patients will then be tilted to 60 degrees for a second time and remain in that position for approximately 15 minutes.
- NE will be drawn approximately 5 minutes after being tilted up to 60 degrees.
- AVP will be drawn approximately 15 minutes after being tilted up to 60 degrees.

Figure 2. **Timeline of Visit 2**



The total time for Visit 2 will be approximately **4-6 hours**, pending observation time post yohimbine administration (see Figure 2 above).

A cardiac electrophysiology sub-investigator, who will be trained in the protocol and drug effects, will monitor the tilt test, as well as halt the test in the unlikely case of dangerous syncope, arrhythmia, or intolerable symptoms. Yohimbine may even improve orthostasis.[65, 66]

Dr. Robbins, or a designated sub-investigator, will be available via pager during all scheduled visit 2 activities. In the event of any adverse events during yohimbine administration and HUT, he will be available to assess and document any adverse effects clinically and identify a plan for clinical treatment, should any be necessary. Any adverse events occurring during yohimbine administration and HUT involving autonomic nervous system function and vital signs will be monitored for at least 3 hours post event to assure stable vital signs/condition.

7.4 Follow-up Phone Call

24-72 hours after Visit 2 has been completed, the subjects will be contacted over the phone and will be enquired about any adverse events following research procedures.

8 Statistical Plan

8.1 Sample Size Determination

Our primary study objective is to compare the nonmotor symptoms of fatigue, anxiety, depression, apathy, and cognitive impairment between the OH and non-OH groups. If we aim to detect a clinically significant difference of 2 points on an 11 point visual analogue fatigue scale, only 4 patients in each group are needed, using a 1-way test of means and assuming a population standard deviation of 1, $\alpha = 0.05$ and $\beta=0.80$. However, it is important to recognize that this is an investigative pilot study; since little research has been done in this area and we cannot be certain

of these assumptions, it is entirely possible the study will be underpowered for at least some of our primary and secondary outcomes.

8.2 Statistical Methods

Primary analysis plan:
To test whether OH correlates with the nonmotor symptoms of fatigue, anxiety, depression, apathy, and cognitive impairment, we will compare these variables between the PD (+OH) group to the PD (-OH) group using the Mann-Whitney *U* test. Although this pilot study is likely underpowered for additional analyses, we will then construct several linear regression models with each nonmotor variable as an outcome, and also include important clinical (e.g. disease duration, total LDED) and demographic variables in the models in order to test if OH is independently associated with these nonmotor outcomes.

Secondary analysis plan:
To test whether central NA dysfunction is involved in these nonmotor symptoms, we will correlate each variable (i.e. quantified scores of depression, apathy, anxiety, fatigue, and cognition) with the difference before and after yohimbine in the change in catecholamine and AVP levels supine and at 60 degree tilt. We will also correlate the nonmotor scores with pupillary redilation speed, which measures sympathetic function, before and after yohimbine. We will compare change in anxiety, mood, and fatigue scores (measured on a visual analogue scale) before and after yohimbine between the PD (OH+) and PD (OH-) groups using the Mann-Whitney *U* test. We will also compare the changes in BP parameters before and after yohimbine between groups.

After these initial correlations and comparisons, we will construct linear regression models incorporating clinical and demographic variables of interest in order to test if our measures of NA dysfunction independently predict the nonmotor symptoms of PD, though we expect these analyses to be underpowered. Finally, we will test if central NA dysfunction (measured through changes in catecholamines and pupillary response to yohimbine, as above) explains the relationship between OH and the nonmotor symptoms of PD by incorporating our measures of central NA dysfunction into the linear regression models described above, and testing whether the relationship between OH and nonmotor symptoms persist.

8.3 Subject Population(s) for Analysis

All subjects who complete at least one study visit will be subjected to the study analysis.

9 Safety and Adverse Events

9.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the end of study treatment follow-up is defined as the completion of the follow-up phone call.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period and are determined to be possibly related to the study treatment or study participation must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others

(See definitions, section 9.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

9.3.1 Investigator reporting: notifying the Dartmouth IRB

This section describes the requirements for safety reporting by investigators who are Dartmouth faculty, affiliated with a Dartmouth research site, or otherwise responsible for safety reporting to the Dartmouth IRB. The Dartmouth Hitchcock Health IRB requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Dartmouth IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

1. Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.
2. Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Dartmouth IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths:
Concerning deaths that occur during the course of a research study:

- Report the event when the death is unforeseen (unexpected) and possibly related indicating participants or others may be at increased risk of harm. The AE/Unanticipated Problem Form is required.
- Report the event at the time of continuing review, for all other deaths, regardless of whether the death is related to study participation.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the Dartmouth IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality

- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

9.3.2 Sponsor reporting: Notifying the FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days***
  Any study event that is:
  - associated with the use of the study drug
  - unexpected, and
  - fatal or life-threatening

- ***Within 15 calendar days***
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements

Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

Division of Neurology Products
10903 New Hampshire Avenue
Silver Spring, MD 20993
Building 22, Suite 4346
Phone: (301) 796-2250 Fax**:** (301) 796-9842

9.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. In addition to PI oversight, a medical monitor external to the study team will be identified. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

10 Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects'

diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.3 Case Report Forms

Both written study case report forms (CRF) and RedCap will be data collection instruments for this study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the questions was not asked, a written notation will be made. If an item is not applicable to the individual case, written notation will be made. All changes made to written CRF's will be initialed and dated. Changes made to data recorded in RedCap will be recorded by an audit trail.

10.4 Records Retention

Records will be retained for 10 years following publication of results from the study.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and Dartmouth compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Dartmouth compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

This study is being funded by the Dartmouth-Hitchcock Department of Neurology.

13.2 Conflict of Interest

All Dartmouth investigators will follow the Dartmouth conflict of interest policy.

13.3 Subject Stipends or Payments

Subjects will be paid $60 after all study visits have been completed.

14 ATTACHMENTS

14.1 References

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14.2 Drug Insert

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

YOCORAL 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yohimbine hydrochloride .... 5 mg per tablet.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL DATA

4.1. Therapeutic indications

Adjunctive treatment of erectile dysfunction.

4.2. Dosage and method of administration

Dosage

3 to 4 tablets a day in 3 doses.
The dosage will be adapted according to the individual results, without exceeding 4 tablets per day (ie 20 mg / day).
A delay of 2 to 3 weeks may be necessary to see the first effects of treatment appear.
In patients with renal and / or hepatic impairment
Patients with mild to moderate renal and / or hepatic impairment should use Yocoral with caution (see section 4.4). Yocoral is contraindicated in patients with Hepatic and / or severe renal impairment (see section 4.3).
In the geriatric patient
There is great variability in the plasma distribution of yohimbine. Peak plasma concentration and the AUC of the active 11-OH-yohimbine metabolite may be decreased in elderly patients (see section 5.2). The clinical relevance of the use in geriatric patients is not known.
Pediatric population
Yocoral is not indicated for patients under 18 years of age.
Women
Yocoral is not indicated for sexual dysfunction in women.

Administration mode

The tablets should be taken with a glass of water, preferably removed from meals.

4.3. Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Severe hepatic and / or renal insufficiency,
• Heart disease (including coronary heart disease, tachyarrhythmia),
• Hypertension, hypotension

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• Psychiatric disorders, particularly emotional and panic disorder,
• gastrointestinal ulcer,
• Glaucoma,
• Concomitant use of products acting on the central nervous system (eg drugs treating psychiatric or neurological disorders, some antihypertensives, alcohol).

4.4. Special warnings and precautions for use

• It is not recommended to use yohimbine for erectile dysfunction caused by serious psychological or organic illness, or if the disease is of organic origin clearly correctable.
• There has been a report of increased epileptic seizures when yohimbine was used with concomitant treatment for epilepsy. Therefore, it can not be excluded that yohimbine might promote epileptic seizures in epileptic patients.
• Yohimbine may aggravate existing renal dysfunction.
• Impairment of liver function may influence the biotransformation of yohimbine and thus reinforce its clinical effects or its undesirable effects.
• The effect of the combination of yohimbine with other drugs used in the treatment of Erectile insufficiency is not known. As a result, an interaction potentiating the effects undesirable effects can not be excluded.

4.5. Interactions with other drugs and other forms of interactions

Associations advised against

+

Central antihypertensives

Possible inhibition of antihypertensive activity by antagonism at the receptors. The Yohimbine and clonidine should not be administered concurrently as their effects may be neutralize.

Associations to take into account

+

antidepressants

Concomitant use of yohimbine and antidepressants may enhance effects and effects adverse effects of both drugs.
It has been reported an interaction with imipramine antidepressants, clomipramine, amitriptyline and fluoxetine. Clomipramine increases plasma levels of yohimbine and can potentiate the effects of drugs.

+

alprazolam

Yohimbine antagonizes the effects of alprazolam on behavior, biochemistry and pressure arterial at the healthy subject.

+

phenothiazine

An interaction with phenothiazine is possible.

+

amphetamines

Concomitant use of yohimbine and amphetamines should be avoided due to potentially strengthened.

+

opioids

Yohimbine may enhance the effect of opioids.

+

sibutramine

Patients with cardiovascular risk factors should avoid use concomitant with anorectics containing sibutramine. This can lead to tachycardia and hypertension.

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4.6. Fertility, pregnancy and lactation

Pregnancy

YOCORAL has no indication in women.

feeding

YOCORAL has no indication in women.

Fertility

The effect of yohimbine on fertility has not been studied. Preclinical data did not show effects on fertility (see section 5.3).

4.7. Effects on ability to drive and use machines

Due to the variability of the individual reaction of yohimbine on the central nervous system, Yocoral may impair the ability to drive and use machines, including association with alcohol consumption.

4.8. Side effects

Adverse effects are predominantly dose-dependent and attributed to pharmacological effects of the drug.

The side effects listed below are classified according to their frequency of occurrence:

• very common (≥ 1/10)
• common (≥ 1/100, <1/10)
• uncommon (≥ 1/1000, <1/100)
• rare (≥ 1/10 000, <1/1000)
• very rare (<1 / 10,000)
• indefinite frequency (can not be estimated based on available data)

Blood and lymphatic system disorders

• *Not known* : agranulocytosis

Immune system disorders

• *Uncommon:* allergic reactions

Psychiatric disorders

• *Common:* insomnia, anxiety, agitation, irritability, impatience
• *Uncommon:* nervousness, decreased libido

Nervous system disorders

• *Common* : headache
• *Uncommon* : dizziness, cold feet, paresthesia
• *Very rare* : tremors

Heart conditions

• *Uncommon:* palpitations, tachycardia, increased heart rate

Vascular disorders

• *Uncommon:* increased blood pressure, hypotension
• *Not known* : persistent priapism

Respiratory, thoracic and mediastinal disorders

• *Very rare* : bronchospasm

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Gastrointestinal disorders

• *Common* : nausea

• *Uncommon* : vomiting, anorexia, gastrointestinal disturbances (epigastric pain, diarrhea, reflux, constipation, flatulence)

Skin and subcutaneous tissue disorders

• *Uncommon:* redness of the skin, rash, hives, hirsutism

• *Very rare:* exanthem

Renal and urinary disorders

• *Frequent:* increased urinary frequency.

• *Very rare:* dysuria, decreased urinary urgency, genital pain

General disorders

• *Uncommon:* Sweating, chills, fever, fatigue

Reporting of suspected adverse reactions

The reporting of suspected side effects after approval of the drug is important. It allows continuous monitoring of the benefit / risk ratio of the drug. Please report any suspected adverse reactions via the national reporting system: National Agency of medicines and health products (ANSM) and a network of regional centers for Pharmacovigilance - Website: www.ansm.sante.fr.

4.9. Overdose

The following symptoms appeared after a massive overdose (0.2 - 5 g) of yohimbine: toxic symptoms with nausea, epigastric pain, vomiting, diarrhea, tingling, chills,flushing, psycho-organic syndrome with anxiety, confusion, unconsciousness, incoordination, seizures, somnolence, hypertension and / or hypotension, tachycardia, retrosternal pain, atrial fibrillation, retrograde amnesia, vegetative disorders, cyanosis, urinary retention, systemic lupus erythematosus.

Treatment of overdose:

After ingestion of high doses, in the acute phase, detoxification with gastric lavage is recommended followed by the administration of medicinal charcoal, and a medicinal support therapy according to the clinical course: anticonvulsant treatment, benzodiazepines in case of administration massive. Clonidine can inhibit psychovegetative symptoms. If necessary, intubation, mechanical ventilation and catheterization of the bladder.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: DRUGS USED IN ERECTILE DISORDERS, ATC code: G04BE04 (genitourinary system and sex hormones).

Yohimbine hydrochloride is a competitive antagonist of alpha-2-adrenergic receptors with a low affinity for alpha-1-adrenergic α1 receptors, depending on its location. The affinity for Alpha-2 receptor subtypes can vary between tissues / organs and species. The action of yohimbine hydrochloride on other receptors known for their activity on erection is discussed below, including antagonistic properties at dopamine D2 receptors, and receptor activity Serotoninergic 5-HT1A, B, D, and vaso-intestinal cholinergic and polypeptic receptors.

The mechanism of erection and the precise mode of functioning of yohimbine in erectile dysfunction is not yet fully understood. Action on the central nervous system responsible for erection through effects on the autonomic nervous system is discussed. In addition, yohimbine seems to act on the dilation of the blood vessels of the penis and directly on the penile tissue.

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Norepinephrine binding to pre-junctional adrenergic receptors on adrenergic, cholinergic and on non-adrenergic / non-cholinergic nerves that regulate negatively the release of norepinephrine and nitric oxide, respectively. Inhibition of this
feedback from yohimbine hydrochloride, a alpha2 receptor antagonist, leads to an increase in the release of norepinephrine and nitric oxide respectively.
In smooth muscle tissue, the binding of adrenaline and norepinephrine to
adrenergic α2 receptors induces contraction via inhibition of adenylate cyclase by a G-protein coupled receptor.
Inhibition of α2 penile adrenergic receptors by yohimbine hydrochloride
and stimulation of nitric oxide release increases the relaxation of smooth muscle and decreases contraction, resulting in erection.
Due to the norepinephrine stimulating effect of yohimbine hydrochloride, it may
influence or aggravate (pre-existing) pathologies related to the noradrenergic system. In this
context, yohimbine hydrochloride is psychoanaleptic and can cause anxiety. Furthermore,
increased noradrenaline release and sympathetic activation affect the cardiovascular system. A rise in blood pressure and heart rate has been described, with an increase in impulse errors and accelerated reaction times after the increase in the release of norepinephrine associated with yohimbine. Norepinephrine leads to activation
of β1 receptors in the heart and peripheral vessels, respectively, with aconsequence of vasoconstriction. Notably, the individual response seems to depend on physiology, because yohimbine hydrochloride caused a lower rate increase plasma levels of noradrenaline in hypertensive patients than in normotensive subjects, but
the vasopressive response was stronger in hypertensive patients. An alteration of the balance of
α adrenergic receptors, for example, with desensitization of α2 adrenergic receptors pre-
synaptic activity and hyperreactivity of post-synaptic α1 receptors, which may lead to
development of hypertension, and could be an explanation of these different responses. In
some patients with severe orthostatic hypotension, significant increases in
systolic blood pressure could be observed after the administration of hydrochloride yohimbine (5.4 mg).
However, patients with panic disorders can have an anxiety and cardiovascular response to yohimbine hydrochloride, probably because of the noradrenergic dysregulation and the higher density and sensitivity of α2 receptors.
In addition, the activation of α2 receptors results in the inhibition of various gastrointestinal functions,
including gastric motility and emptying, gastrointestinal secretions, and acetylcholine release
by the vagus nerve. Therefore, yohimbine hydrochloride as a competitive inhibitor of
a2 adrenergic receptors could increase the release of acetylcholine and gastric secretion.
Finally, yohimbine hydrochloride could influence the release of vasopressin
antidiuretic, ADH) induced by the noradrenergic system. On the one hand, it has been shown that
Yohimbine hydrochloride inhibits catecholamine-induced ADH release. On the other hand, it is
known that yohimbine hydrochloride increases the plasma level of noradrenaline and that it can
inhibit diuresis induced by medetomidine, a α2-adrenergic agonist. Therefore, an effect
on urination in humans is possible but has not yet been elucidated. In accordance with the heterogeneous effect on the inhibition of norepinephrine binding while increasing the concentration of noradrenaline, the reactions may depend on the individual initial state.

5.2. Pharmacokinetic properties

Absorption

Yohimbine hydrochloride is completely absorbed in about one hour. Mmaximum blood levels are reached after 45 to 120 minutes. The bioavailability varies enormously with between individuals and in the same individual, primarily because of a first-pass effect hepatic.

Distribution

The distribution of yohimbine hydrochloride indicates a high tissue binding capacity. Yohimbine has a plasma protein binding of approximately 82%. Only a small amount of
yohimbine hydrochloride and the active metabolite 11-hydroxyyohimbine is detectable in cerebrospinal fluid.

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biotransformation

Two hydroxyl metabolites could be determined: 10-hydroxyyohimbine and the active metabolite 11-hydroxyyohimbine.

Elimination

The product is eliminated by the hepatic and extra-hepatic metabolic pathways. The half-life varies between 0.25 and 2.5 hours after a single dose. The active metabolite 11-hydroxyyohimbine has a higher elimination half-life of about 6 hours.

Special characteristics in elderly subjects

Maximum plasma concentrations and area under the curve (AUC) of the active 11-OH-metabolite yohimbine were significantly lower in 10 elderly subjects (71.2 ± 3.5 years), compared with to 11 young volunteers (26.3 ± 4.8 years), and 10 patients with Alzheimer's disease (69.5 ± 7.9 years). There is great variability in the plasma distribution of yohimbine. Clinical relevance of use in the elderly is not assessable.

5.3. Preclinical safety data

Very limited preclinical data on chronic toxicity showed an absence of organic lesions in the rat, although dose-dependent weight gain was observed. The tests *in vitro* and *in vivo* for genotoxic potential of yohimbine were negative. Yohimbine showed no effect on fertility or reproductive behavior in male rats as part of a fertility study. At doses greater than 6 mg / kg body weight, a reduction of testes and epididymal weight was observed.

6. PHARMACEUTICAL DATA

6.1. List of excipients

Calcium hydrogen phosphate dihydrate, povidone K25, microcrystalline cellulose, corn starch, magnesium stearate, colloidal anhydrous silica.

6.2. incompatibility

Not applicable.

6.3. The duration of the conversation

3 years

6.4. Special precautions for storage

Store at a temperature not exceeding 25 ° C.

6.5. Nature and contents of the pack

50 or 100 tablets in platelets (PVC / Aluminum) of 10 tablets.

6.6.

Special precautions for disposal and handling

No special requirements.

7. HOLDER OF THE MARKETING AUTHORIZATION

CHEPLAPHARM ARZNEIMITTEL GMBH

ZIEGELHOF 24
GREIFSWALD 17489
GERMANY

CIS: 6 981 627 6 2018042700224
Format T10 - Q11ADOC034 v.05
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8. MARKETING AUTHORIZATION NUMBER (S)

• 34009 353 730 9 0: 50 tablets in platelets (PVC / Aluminum).
• 34009 353 731 5 1: 100 tablets under pads (PVC / Aluminum).

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

Date of first authorization: March 28, 2000
Last renewal date: March 28, 2010

10. DATE OF REVISION OF THE TEXT

04/2018

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.