

PROTOCOL

Safety and Efficacy of Droxidopa for Fatigue in Patients with Parkinsonism

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Study Title:

Safety and Efficacy of Droxidopa for Fatigue in Patients with Parkinsonism

Background/Rationale:

Fatigue is a common debilitating symptom in neurological disorders, and over 50% of Parkinson's disease (PD) patients report fatigue as one of their top three debilitating symptoms. The definitions of fatigue are subjective, but they all focus on having an abnormal lack of energy that interferes with normal function [2]. Currently, there are no evidence-based guidelines for treating fatigue in PD, and no effective medications or therapeutic modalities exist for fatigue symptoms in patients with PD. Multiple medications are being tried with no evidence in double-blind clinical trials. One study showed a statistically significant improvement with methylphenidate, but no effect was seen when data from other stimulant trials were pooled. A post hoc analysis of rasagiline showed statistically but clinically insignificant improvements, and levodopa showed small benefits for fatigue. However, non-motor symptoms were not the primary endpoints of the study, and further research is required to better understand and treat fatigue in PD. We hypothesize that fatigue is due to diminished levels of norepinephrine in PD. The locus coeruleus (LC), one of the major sources of norepinephrine, is affected during the preclinical phase of PD during stage 2 of Braak pathology staging. Norepinephrine is the final metabolite of dopamine, and we hypothesize that by adding exogenous norepinephrine, we can control some of the motor and non-motor symptoms of Parkinsonism. Norepinephrine is the final metabolite of droxidopa, and it is still unclear if it passes the blood-brain barrier. Here, we propose a pilot study to explore our hypotheses and to measure the efficacy and safety of droxidopa in Parkinsonism patients with fatigue.

Scientific Value:

Randomized control studies addressing fatigue in patients with Parkinsonism are an insufficiently addressed requirement to understand how to improve quality of life outcome measures. The lack of progress in understanding the pathophysiology and treatment of fatigue, along with the absence of effective therapy for fatigue in patients with Parkinsonism argues for a greater effort. The goal of the proposed pilot study is to follow patients over 6 months total (with 3 months of it being an open-label trial). The outcomes of our study will help determine the efficacy of droxidopa for fatigue in patients with Parkinsonism. Additionally, the outcomes of our study will provide us important information regarding the efficacy of droxidopa on other non-motor and motor symptoms of Parkinsonism.

Primary Product:

Droxidopa

(Droxidopa is also known as L-threo-3,4-dihydroxyphenylserine, or L-DOPS. Droxidopa is decarboxylated by 3,4-dihydroxyphenylalanine (DOPA) decarboxylase (DDC), and is directly converted to Nor Epinephrine. There are four stereoisomers of L-DOPS; however, only the L-threo-enantiomer (droxidopa) is biologically active. It is the International Non-proprietary Name (INN) for a synthetic amino acid precursor of NE, which was originally developed by Sumitomo Dainippon Pharmaceuticals Co., Limited, Japan (SDP). It has been approved for use in Japan since 1989 and in the United States (US) since February 2014).

Safety Profile

Droxidopa is safe and well tolerated in patients with symptomatic Neurogenic Orthostatic Hypotension associated with primary autonomic failure (PD, MSA and PAF), Dopamine Beta Hydroxylase Deficiency, or Non Diabetic Autonomic Neuropathy. Data from this program indicates that droxidopa treatment is associated with a small increase in supine hypertension (SBP >180 mmHg), and an increase in the incidence of headaches, dizziness, and nausea. Data from the SDP-sponsored clinical studies conducted in Europe and the large safety database of patients treated in Japan, where droxidopa has been marketed for over 20 years, further support the safety of droxidopa. Community standards do not require lab work, including pregnancy tests, when initiating or maintaining therapy with Droxidopa.

Primary Study Objective:

- To determine the efficacy of droxidopa for fatigue in patients with Parkinsonism measured by the Visual Analog Fatigue Scale (VAFS).
 - Subjects will complete the VAFS which measures level of fatigue with zero being equivalent to energetic with no fatigue to ten being worst possible fatigue. The focus will be on change between baseline and 12 weeks, change between 13 weeks and 25 weeks, and at 29 weeks.

Secondary Study Objectives:

- To determine the efficacy of droxidopa on motor and non-motor symptoms of Parkinsonism using the Unified Parkinson's Disease Rating Scale (UPDRS).
 - The UPDRS is a composite measurement of motor and non-motor symptoms divided into six domains. Domain I measures Mentation, Behavior and Mood. Domain II measures Activities of Daily Living. Domain III measures Motor Examination. Domain IV measures Complications of Therapy. Domain V is Modified Hoehn and Yahr Staging. Domain 6 is Schwab and Engladn Activities of Daily Living Scale. The focus will be on change between baseline and 12 weeks, change between 13 weeks and 25 weeks, and at 29 weeks.

Study Method/Design:

This is a pilot study which will include 32 subjects total; with 16 Parkinsonism patients initially assigned to droxidopa treatment (group 1, experimental) and 16 Parkinsonism patients initially assigned to placebo (group 2, control). At no point during this study will there be any blood draws or urine collections. Patients will not be instructed to measure their blood pressure at home, and will instead be instructed to contact their primary doctor or study doctor if they experience any new symptoms. At the next study visit, these symptoms will be assessed and recorded.

Within each group (n=16 per group), half (n=8 per group) will be Parkinsons Disease (PD) patients and half (n=8 per group) will be patients with atypical Parkinsonism to include multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). Overall, the study will recruit 16 PD patients and 16 patients with MSA or PSP. The Principal Investigator (PI)/ Sub Investigator will recruit subjects from the Faculty Medical Office (FMO) Movement Disorders Clinic at Loma Linda University, Loma Linda, California where several hundred patients who are clinically diagnosed with Parkinsonism are seen per year. Patients will not be recruited by phone.

Table 1 (on Page 7 of this protocol) describes how the study will be conducted. This is a randomized, placebo-controlled, double-blind clinical trial for 3 months, and after a wash-out period of 7 days, every subject will receive droxidopa for another 3 months during the open-label phase. This approach will provide us with the chance to evaluate the efficacy of droxidopa for as long as 6 months. There will be one follow up visit that occurs 4 weeks after the final 6 month visit when Droxidopa has been withdrawn to evaluate fatigue in the absence of droxidopa. Subjects who meet the inclusion/exclusion criteria and consent to participating in the study will be randomized to the experimental group (droxidopa treatment for the entire 6 months) or control group (placebo for first 3 months then droxidopa treatment for the remaining 3 months) by a random number generator. Subjects and the Principal Investigator/ Sub Investigator will be blinded to the group allocation for the first 3 months of the study. During the first 3 months of the double-blind phase, both groups will titrate (either droxidopa for the experimental group or placebo for the control group) then continue their optimal dose for 3 months. After a 7-day wash-out period, both groups will titrate again (droxidopa only this time), then continue their optimal dose for another 3 months during the open-label phase.

We will perform detailed assessments (see table 1) for the primary and secondary efficacy outcomes at 6 different visits, including the first screening/ baseline visit.

Visit 1 will be screening/ baseline visit, where informed consent and demographics will be taken, it will also include a complete physical examination and vitals along with orthostatic standing test will also be taken. History of intake of concomitant medications, prohibited medications, and recent diagnostic, therapeutic or surgical procedures, will be taken. Medications taken in the 28 days prior to study will be recorded. It will be

during this visit that the droxidopa or placebo will be distributed and the titration will begin. VAFS and UPDRS will be completed at this visit.

Visit 2 will occur 6 weeks from screening, and medication titration will finish prior to this day. History of intake of concomitant medications, any adverse events, physical exam, vital signs, adherence to treatment regimen including avoidance of prohibited medications, and recent diagnostic, therapeutic or surgical procedures, will be recorded and VAFS and UPDRS will be completed. IMP will be dispensed and compliance and capsule count will be done on this visit and remaining IMP will be returned.

Visit 3 will occur 6 weeks from Visit 2 and correspond with the maintenance period. Again history of intake of concomitant medications, any adverse events, physical exam, vital signs, adherence to treatment regimen including avoidance of prohibited medications, and recent diagnostic, therapeutic or surgical procedures will be recorded, and VAFS and UPDRS will be completed. Compliance and capsule count will be done on this visit too and remaining IMP will be returned. Patients will be instructed to stop taking their IMP following this visit and IMP will be not be dispensed.

Visit 4 will occur 1 week from Visit 3 and will begin the open-label titration. The patients will not be taking IMP for 7 days (plus 0-14 days) prior to visit 4 to create a washout period. Again history of intake of concomitant medications, any adverse events, physical exam, vital signs, adherence to treatment regimen including avoidance of prohibited medications, and recent diagnostic, therapeutic or surgical procedures will be recorded and VAFS and UPDRS will be completed. IMP (droxidopa only, no placebo) will be distributed and the titration will begin.

Visit 5 will occur 6 weeks from Visit 4 and will and medication titration will finish prior to this day. History of intake of concomitant medications, any adverse events, physical exam, vital signs, adherence to treatment regimen including avoidance of prohibited medications, and recent diagnostic, therapeutic or surgical procedures, will be recorded and VAFS and UPDRS will be completed. IMP will be dispensed and compliance and capsule count will be done on this visit and remaining IMP will be returned.

Visit 6 will occur 6 weeks after Visit 5 and will correspond with the maintenance period. Again history of intake of concomitant medications, any adverse events, physical exam, vital signs, adherence to treatment regimen including avoidance of prohibited medications, and recent diagnostic, therapeutic or surgical procedures will be recorded, and VAFS and UPDRS will be completed. Compliance and capsule count will be done on this visit too and remaining IMP will be returned. Patients will be instructed to stop taking their IMP following this visit and IMP will be not be dispensed.

Visit 7 will be final visit which will happen 4 weeks after visit 6 to evaluate fatigue in the absence of droxidopa. History of intake of concomitant medications, any adverse events, physical exam, vital signs, and recent diagnostic, therapeutic or surgical procedures, will be recorded, and VAFS and UPDRS will be completed at this visit.

Table 1

Study Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening/ Baseline	Double blinded Titration	Double blinded Maintenance	Washout	Open-Label Titration	Open-Label Maintenance	Final Visit
Interval	Time 0	6 weeks (+ 0-14 days)	6 Weeks (+ 0-14 days)	1 week (+ 0-14 days)	6 Weeks (+0-14 days days)	6 Weeks (+0-14 days days)	4 Weeks (+0-14 days days)
Time from Baseline	Time 0	6 weeks from baseline	12 weeks from baseline	13 weeks from baseline	16 weeks from baseline	25 weeks from baseline	29 weeks from baseline
Written Informed consent	X						
Review inclusion and exclusion criteria	X						
Demography	X						
Concomitant medication	X	x	X	x	X	X	X
Adverse events (continuous monitoring)		x	X	x	X	X	X
Physical examination	X	x	X	x	X	X	X
Vital signs (BP, HR, RR, temp) and weight	X	x	X	x	X	X	X
Orthostatic Standing Test	x						
Dose titration evaluation		x			x		
VAFS	x	x	X	x	X	X	X
UPDRS	x	x	X	x	X	X	X
Randomization	x						
Unblinding			x				
Blinding	x						
IMP dispensed	x	x		x	x		
Capsule count / compliance check		x	X		x	x	
IMP returned		x	x		x	x	

Use of Concomitant, Prior, and Prohibited Medications

• Concomitant Medications

No prescribed concomitant medication is to be taken without the knowledge of the Investigator. The Investigator may, at their discretion, prescribe any medication considered necessary for the patient's welfare that is not expected to interfere with the evaluation of the IMP. All concomitant medications must be recorded. The generic name of the drug, dose, frequency of dose and the duration of treatment must be specified. In addition, any diagnostic, therapeutic or surgical procedure conducted during the study, that is not part of the study, should be recorded. The date, indication, description of procedure(s) and any clinical finding should be recorded.

All concomitant medications should be maintained at stable doses during the study. If patients are already on other concomitant medications, which based on investigator judgment, would be expected to have side effect of hypertension, (e.g, amphetamine, amphetamine-like drugs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine reuptake inhibitors (NRIs), evaluate their continued use when introducing droxidopa.

• Prior Medications

Prior medication includes all medications (including herbal treatments and vitamins) taken within 28 days prior the Screening Visit . All prior medications taken within 28 days of the Screening Visit must be recorded.

• Prohibited Medications

Administering droxidopa in combination with other agents that increase blood pressure (e.g, norepinephrine, ephedrine, midodrine, triptans) would be expected to increase the risk for supine hypertension. The following drugs must not be prescribed by the Investigator or taken by patients during the study:

- Vasoconstricting agents such as ephedrine, dihydroergotamine, or midodrine;
- Sumatriptan-like drugs, (for example, naratriptan, zolmitriptan, rizatriptan);
- Cyclopropane or halothane, or other halogen-containing inhalational anesthetics;
- Catecholamine-containing preparations (e.g. isoprenaline);
- Non-selective monoamine oxidase inhibitors (MAOIs) including linezolid;
- Ergotamine derivatives (except if anti-Parkinsonian medication);
- Drugs that have anti-hypertensive properties and, in the Investigator's opinion, significantly contribute to the patient's orthostatic hypotension; and
- Any investigational medication.

Patients currently taking a prohibited medication at Screening may be enrolled into the study after a washout of at least 5 half-lives prior to first dose of IMP.

Inclusion Criteria (All Patients)

1. Age of 50 years or older.
2. Clinical diagnosis of Parkinsons Disease or Atypical Parkinsonism (including MSA, PSP)
3. Patients should be fluent and be able to understand and converse freely in English.
4. Patient should report fatigue as a symptom and must have a mean VAFS score of 4 or more at baseline.
5. Provide written informed consent to participate in the study and understand that they may withdraw their consent at any time without prejudice to their future medical care.

Exclusion Criteria (All Patients)

1. In the Investigator's opinion, the patient is not able to understand or cooperate with study procedures.
2. Known or suspected alcohol or substance use disorder within the past 12 months (as per DSM-5 criteria)
3. Women who are pregnant or breastfeeding
4. Women of childbearing potential (WOCP)
5. Sustained supine hypertension greater than or equal to 180 mmHg systolic or 110 mmHg diastolic. Sustained is defined as the average of 3 observations each at least 10 minutes apart with the patient having been supine and at rest for at least 5 minutes prior to each measurement.
6. Untreated closed angle glaucoma
7. Diagnosis of hypertension that requires treatment with antihypertensive medications
8. Any significant uncontrolled cardiac arrhythmia.
9. History of myocardial infarction, within the past 2 years.
10. Current unstable angina.
11. Congestive heart failure (NYHA Class 3 or 4).
12. Diabetic autonomic neuropathy.

13. History of cancer within the past 2 years other than a successfully treated, non-metastatic cutaneous squamous cell or basal cell carcinoma or cervical cancer in situ.
14. Gastrointestinal condition that may affect the absorption of Investigational Medicinal Product (e.g. ulcerative colitis, gastric bypass).
15. Any major surgical procedure within 30 days prior to the first titration visit.
16. Currently receiving any investigational drug or have received an investigational drug within 28 days prior to the first titration visit.
17. Any condition or laboratory test result, which in the Investigator's judgment, might result in an increased risk to the patient, or would affect their participation in the study.
18. The Investigator has the direction to exclude a patient if, for any reason, they feel the patient is not a good candidate for the study or will not be able to follow study procedures.
19. We will also exclude patients with dementia or non-treated depression, because fatigue may be associated with these conditions, and these patients may be less reliable at completing assessments and with medication compliance.
20. Subjects who have a mean VAFS score of less than 4 at baseline will be excluded from the study.
21. We will exclude vulnerable populations from this study.
22. Patients with uncontrolled intercurrent illnesses including, but not limited to severe lung disease, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic cardiac arrhythmia, and situations that would limit compliance with study requirements will be excluded.
23. Orthostatic hypotension (OH) will be excluded from this study.

Exit Criteria

Patients will be removed from the study if the patient has any side effects, or the patient feels uncomfortable continuing the study for any reason or physician feels patient is not safe to continue study.

Early Termination Visit

If at any time during the study a patient requests to withdraw from treatment, or if a decision is made to withdraw the patient, the patient will be requested to return for an

early termination visit. A decision will be made to withdraw the patient from the study while on site due to non-adherence to the plan as detailed in the protocol, the development of any adverse effects, the development of any of the above stated exclusion criteria, or due to starting any of the prohibited medications for this study. The early termination procedures should be completed during that visit. The patient should not be brought back for an Early Termination Visit at a later date.

Whenever practical, patients should be encouraged to remain on IMP until the completion of the early termination procedures. This is particularly important for patients who withdraw from the study during the double-blind treatment period. As the primary efficacy endpoint is time to intervention, it is critical that the date of withdrawal (which will be the date of the patient's last dose) due to a need for intervention during the double-blind period is accurately recorded.

The Investigator or qualified designee will conduct the following procedures and record the data.

- Record the time and dose of IMP taken on the day of the visit
- Record the reason for withdrawal
- Review of AEs
- Review of concomitant medication
- Patient stops IMP or withdraws from study for patient-reported lack of efficacy:
- Physical Exam
- Vital signs (supine BP, HR, RR) and weight.
- IMP return and capsule count/compliance check
- Schedule Follow-Up Visit

All patients who discontinue participation in the study are to have a Safety Follow-Up Visit conducted 30 days (+5 days) after their final dose of IMP.

Investigational Medicinal Product and Formulation

- Droxidopa (also known as L-threo-3,4,-dihydroxyphenylserine, or L-DOPS) in 100, 200, and 300mg capsules.
- Placebo capsules (to match Droxidopa 100, 200m, and 300mg capsules)
- Both Placebo and Droxidopa will be titrated in the same schedule

Both Droxidopa and Placebo will be provided by Lundbeck. Both will be stored at ambient temperature in a locked room, in the clinic where the trial is taking place. Medication count and medication temperature will be logged.

Dosage and Administration

During the Titration Period and Open-Label Period, patients will receive 100, 200, 300, 400, 500, or 600 mg TID of droxidopa, orally.

The droxidopa starting dose for all eligible patients in the Titration Period is 100mg TID. Doses will be titrated by 100mg TID; increments will be made weekly until the optimal dose is achieved. Five dose changes are permitted within the first two months of the Open-Label Period. No dose changes are allowed after Visit 3. Optimal dose will be based on patient's subjective response to medication. Patients will be instructed to continue increasing medication until they either A) achieve the maximal dose which is 600mg TID, or B) they do not notice an improvement in their subjective fatigue on a higher dose compared to the most recent dose. Patients will be instructed to measure their blood pressure at least once weekly while titrating the medication. If they do not have a way to measure their blood pressure at home, they will be given the option to come to the clinic for such measurement. If their systolic blood pressure is 140 or above, they will be instructed to contact the study doctor, who will adjust the dose appropriately.

Safety Variables/Measures

Safety will be assessed by reported Adverse Events (AE) and Serious Adverse Events (SAE) and vital signs. Subjects will be asked to monitor their blood pressure at home and report any abnormal changes.

AE/SAE Reporting

Any serious and unexpected adverse events (SAE's) will be reported to the sponsor, FDA, and Loma Linda University (LLU) ethical review board in writing immediately (within 5 days) of the event. Any fatal or life-threatening AEs will be reported to the sponsor, FDA, and LLU ethical review board within 5 days of the event.

- **Recording Adverse Events**

Adverse events (including pre-treatment AEs) must be recorded on an Adverse Event Form. The Investigator must provide information on the AE, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates, intensity; causal relationship to IMP; action taken; and outcome. If the AE is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose). If the intensity changes during the course of an adverse event, this must be recorded on the Adverse Event Intensity Log. If the AE is serious, this must be indicated on the Adverse Event Form. Furthermore, the Investigator must fill out a Serious Adverse Event Report Form and report the SAE to Lundbeck, immediately within 5

days, after becoming aware of it. Adverse events, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

- **Reporting Serious Adverse Events**

The Investigator must report SAEs to Lundbeck immediately (within 5 days) after becoming aware of them by completing a Serious Adverse Event Form.

As much information as possible must be entered when initially completing the Serious Adverse Event Form. If more information about the patient's condition becomes available at a later date, the Serious Adverse Event Form must be updated with the additional information.

The Serious Adverse Event Form will be mailed to:

Global Pharmacovigilance – US
Fax: +1 (847) 282-1003
e-mail: luinc_safety@lundbeck.com

Lundbeck will assume responsibility for reporting SAEs to the authorities in accordance with local regulations. It is the Investigator's responsibility to be familiar with local requirements regarding reporting SAEs to the IRB and to act accordingly. Lundbeck will assess expectedness and inform the Investigators about suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements.

- **Treatment and Follow-Up of Adverse Events**

Patients with AEs must be treated in accordance with usual clinical practice at the discretion of the Investigator. Non-serious AEs must be followed up until resolution or the follow-up assessment whichever comes first. At the safety follow-up visit information on new SAEs, if any and stop dates for previously reported AEs must be recorded. It is the responsibility of the Investigator to follow up on SAEs until the patient has recovered, stabilized, or recovered with sequelae, and to report to Lundbeck all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultations. SAEs that are spontaneously reported by a patient to the Investigator after the follow-up assessment must be handled in the same manner as SAEs that occur during the study. These SAEs will be captured in the Global Pharmacovigilance database.

Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, potential benefits and any potential hazards of the study. No study-related procedures, including washout of any medications, may be performed prior to obtaining written informed consent.

The Investigator must explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time and for any reason. Similarly, the Investigator or Lundbeck is free to withdraw the patient from the study at any time for safety reasons. Any other requirements necessary for the protection of the human rights of the patient will also be explained.

Confidentiality

All patients who provide written informed consent will be assigned a patient number. Subsequently, patients will be identified in the records only by their initials, date of birth, and their patient number (as allowed by local country regulations). Any information published as a result of the study will be such that it will not permit identification of any patient. The information from this study will be available within Lundbeck and may be shared with regulatory authorities. It may also be the subject of an audit by a regulatory agency, such as the Food and Drug Administration (FDA), within the local government. The patient's identity will remain protected except as required for legal or regulatory inquiries.

Data Collection

At each visit, using a data collection form, visit #, subject ID, age, sex, concomitant medication medications, medications taken within 28 days of screening visit, avoidance of prohibited medications, diagnostic, therapeutic or surgical procedure conducted during the study, adherence to regimen vital signs, physical exam, UPDRS score and VAFS score will be recorded and saved in a locked cabinet in a locked room at the neurology clinic where this study is taking place. If Lundbeck requests, they will be provided with protocol, statistical analysis plan, clinical study report, and any other data they request. This material will be provided to Lundbeck in person, not electronically.

Statistics

For VAFS and UPDRS data, mean change from randomization to the end of study in the droxidopa and placebo groups will be compared using analysis of covariance, with value at randomization as covariate and treatment group as main effect. The VAFS and UPDRS are attached to the end of the protocol.

References

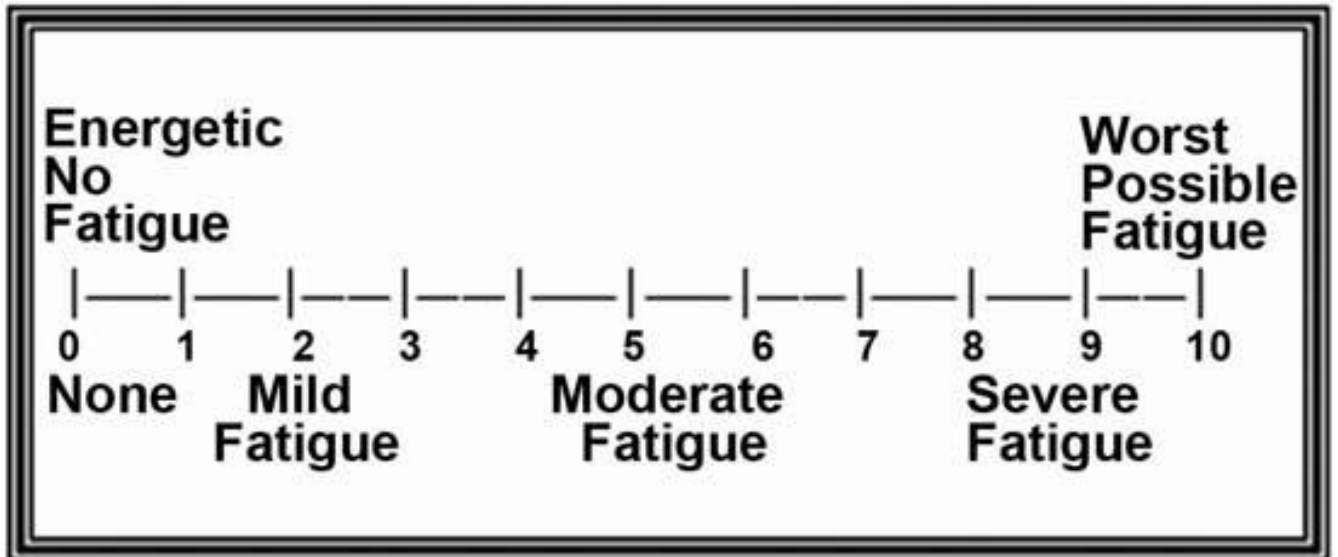
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Appendix I

Questionnaires:

1. Visual Analog Fatigue Scale (VAFS)
2. Unified Parkinson's disease Rating Scale (UPDRS).

Visual Analog Fatigue Scale (VAFS)



Unified Parkinson's Disease Rating Scale

I. Mentation, Behavior and Mood

1. Intellectual Impairment

- 0 = None.
- 1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
- 2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
- 3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
- 4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

- 0 = None.
- 1 = Vivid dreaming.
- 2 = "Benign" hallucinations with insight retained.
- 3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
- 4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression

- 1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
- 2 = Sustained depression (1 week or more).
- 3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
- 4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

- 0 = Normal.
- 1 = Less assertive than usual; more passive.
- 2 = Loss of initiative or disinterest in elective (nonroutine) activities.
- 3 = Loss of initiative or disinterest in day to day (routine) activities.
- 4 = Withdrawn, complete loss of motivation.

II. Activities of Daily Living (for both "on" and "off")

5. Speech

- 0 = Normal.
- 1 = Mildly affected. No difficulty being understood.
- 2 = Moderately affected. Sometimes asked to repeat statements.
- 3 = Severely affected. Frequently asked to repeat statements.
- 4 = Unintelligible most of the time.

6. Salivation

- 0 = Normal.
- 1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
- 2 = Moderately excessive saliva; may have minimal drooling.
- 3 = Marked excess of saliva with some drooling.
- 4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

- 0 = Normal.
- 1 = Rare choking.
- 2 = Occasional choking.
- 3 = Requires soft food.
- 4 = Requires NG tube or gastrostomy feeding.

Unified Parkinson's Disease Rating Scale

8. Handwriting

- 0 = Normal.
- 1 = Slightly slow or small.
- 2 = Moderately slow or small; all words are legible.
- 3 = Severely affected; not all words are legible.
- 4 = The majority of words are not legible.

9. Cutting Food and Handling Utensils

- 0 = Normal.
- 1 = Somewhat slow and clumsy, but no help needed.
- 2 = Can cut most foods, although clumsy and slow; some help needed.
- 3 = Food must be cut by someone, but can still feed slowly.
- 4 = Needs to be fed.

10. Dressing

- 0 = Normal.
- 1 = Somewhat slow, but no help needed.
- 2 = Occasional assistance with buttoning, getting arms in sleeves.
- 3 = Considerable help required, but can do some things alone.
- 4 = Helpless.

11. Hygiene

- 0 = Normal.
- 1 = Somewhat slow, but no help needed.
- 2 = Needs help to shower or bathe; or very slow in hygienic care.
- 3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
- 4 = Foley catheter or other mechanical aids.

12. Turning in Bed and Adjusting Bed Clothes

- 0 = Normal.
- 1 = Somewhat slow and clumsy, but no help needed.
- 2 = Can turn alone or adjust sheets, but with great difficulty.
- 3 = Can initiate, but not turn or adjust sheets alone.
- 4 = Helpless.

13. Falling (Unrelated to Freezing)

- 0 = None.
- 1 = Rare falling.
- 2 = Occasionally falls, less than once per day.
- 3 = Falls an average of once daily.
- 4 = Falls more than once daily.

14. Freezing when Walking

- 0 = None.
- 1 = Rare freezing when walking; may have start hesitation.
- 2 = Occasional freezing when walking.
- 3 = Frequent freezing. Occasionally falls from freezing.
- 4 = Frequent falls from freezing.

15. Walking

- 0 = Normal.
- 1 = Mild difficulty. May not swing arms or may tend to drag leg.
- 2 = Moderate difficulty, but requires little or no assistance.
- 3 = Severe disturbance of walking, requiring assistance.
- 4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)

- 0 = Absent.
- 1 = Slight and infrequently present.
- 2 = Moderate; bothersome to patient.
- 3 = Severe; interferes with many activities.
- 4 = Marked; interferes with most activities.

17. Sensory Complaints Related to Parkinsonism

- 0 = None.
- 1 = Occasionally has numbness, tingling, or mild aching.
- 2 = Frequently has numbness, tingling, or aching; not distressing.
- 3 = Frequent painful sensations.
- 4 = Excruciating pain.

III. Motor Examination

18. Speech

- 0 = Normal.
- 1 = Slight loss of expression, diction and/or volume.
- 2 = Monotone, slurred but understandable; moderately impaired.
- 3 = Marked impairment, difficult to understand.
- 4 = Unintelligible.

19. Facial Expression

- 0 = Normal.
- 1 = Minimal hypomimia, could be normal "Poker Face."
- 2 = Slight but definitely abnormal diminution of facial expression
- 3 = Moderate hypomimia; lips parted some of the time.
- 4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted $\frac{1}{4}$ inch or more.

20. Tremor at Rest (head, upper and lower extremities)

- 0 = Absent.
- 1 = Slight and infrequently present.
- 2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
- 3 = Moderate in amplitude and present most of the time.
- 4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of Hands

- 0 = Absent.
- 1 = Slight; present with action.
- 2 = Moderate in amplitude, present with action.
- 3 = Moderate in amplitude with posture holding as well as action.
- 4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

- 0 = Absent.
- 1 = Slight or detectable only when activated by mirror or other movements.
- 2 = Mild to moderate.
- 3 = Marked, but full range of motion easily achieved.
- 4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands

(Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

Unified Parkinson's Disease Rating Scale

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)

- 0 = Normal.
- 1 = Slow; or may need more than one attempt.
- 2 = Pushes self up from arms of seat.
- 3 = Tends to fall back and may have to try more than one time, but can get up without help.
- 4 = Unable to arise without help.

28. Posture

- 0 = Normal erect.
- 1 = Not quite erect, slightly stooped posture; could be normal for older person.
- 2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
- 3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
- 4 = Marked flexion with extreme abnormality of posture.

29. Gait

- 0 = Normal.
- 1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
- 2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
- 3 = Severe disturbance of gait, requiring assistance.
- 4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

- 0 = Normal.
- 1 = Retropulsion, but recovers unaided.
- 2 = Absence of postural response; would fall if not caught by examiner.
- 3 = Very unstable, tends to lose balance spontaneously.
- 4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)

- 0 = None.
- 1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
- 2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
- 3 = Moderate slowness, poverty or small amplitude of movement.
- 4 = Marked slowness, poverty or small amplitude of movement.

IV. Complications of Therapy

(In the past week)

A. Dyskinesias

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)

- 0 = None
- 1 = 1–25% of day.
- 2 = 26–50% of day.
- 3 = 51–75% of day.
- 4 = 76–100% of day.

33. Disability: How disabling are the dyskinesias?

(Historical information; may be modified by office examination.)

- 0 = Not disabling.
- 1 = Mildly disabling.
- 2 = Moderately disabling.
- 3 = Severely disabling.
- 4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?

- 0 = No painful dyskinesias.
- 1 = Slight.
- 2 = Moderate.
- 3 = Severe.
- 4 = Marked.

35. Presence of Early Morning Dystonia

(Historical information.)

- 0 = No
- 1 = Yes

B. Clinical Fluctuations

36. Are “off” periods predictable?

- 0 = No
- 1 = Yes

37. Are “off” periods unpredictable?

- 0 = No
- 1 = Yes

38. Do “off” periods come on suddenly, within a few seconds?

- 0 = No
- 1 = Yes

39. What proportion of the waking day is the patient “off” on average?

- 0 = None
- 1 = 1–25% of day.
- 2 = 26–50% of day.
- 3 = 51–75% of day.
- 4 = 76–100% of day.

C. Other Complications

40. Does the patient have anorexia, nausea, or vomiting?

- 0 = No
- 1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?

- 0 = No
- 1 = Yes

42. Does the patient have symptomatic orthostasis?

(Record the patient's blood pressure, height and weight on the scoring form)

- 0 = No
- 1 = Yes

V. Modified Hoehn and Yahr Staging

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. Schwab and England Activities of Daily Living Scale

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.

90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.

80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.

70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.

60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.

50% = More dependent. Help with half, slower, etc. Difficulty with everything.

40% = Very dependent. Can assist with all chores, but few alone.

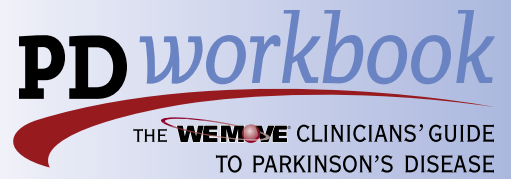
30% = With effort, now and then does a few chores alone or begins alone. Much help needed.

20% = Nothing alone. Can be a slight help with some chores. Severe invalid.

10% = Totally dependent, helpless. Complete invalid.

0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

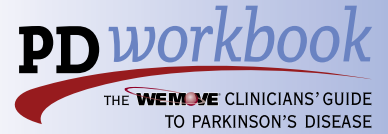
Unified Parkinson's Disease Data Form



Name _____ Unit Number _____

Date																	
DOPA mg/day	hrs DOPA lasts																
		ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
1. Mentation																	
2. Thought Disorder																	
3. Depression																	
4. Motivation/Initiative																	
Subtotal 1-4 (maximum = 16)																	
5. Speech																	
6. Salivation																	
7. Swallowing																	
8. Handwriting																	
9. Cutting food																	
10. Dressing																	
11. Hygiene																	
12. Turning in bed																	
13. Falling																	
14. Freezing																	
15. Walking																	
16. Tremor																	
17. Sensory symptoms																	
Subtotal 5-17 (maximum = 52)																	
18 Speech																	
19. Facial expression																	
20. Tremor at rest: face,lips,chin																	
Hands: right																	
left																	
Feet: right																	
left																	
21. Action tremor: right																	
left																	
22. Rigidity: neck																	
Upper extremity: right																	
left																	
Lower extremity: right																	
left																	

Unified Parkinson's Disease Data Form



Date																
	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
23. Finger taps: right																
left																
24. Hand grips: right																
left																
25. Hand pronate/supinate: right																
left																
26. Leg agility: right																
left																
27. Arise from chair																
28. Posture																
29. Gait																
30. Postural stability																
31. Body bradykinesia																
Sub-total:18-31 (maximum=108)																
Total points: 1-31 (max=176)																
32. Dyskinesia (duration)																
33. Dyskinesia (disability)																
34. Dyskinesia (pain)																
35. Early morning dystonia																
36. "Offs" (predictable)																
37. "Offs" (unpredictable)																
38. "Offs" (sudden)																
39. "Offs" (duration)																
40. Anorexia, nausea, vomiting																
41. Sleep disturbance																
42. Symptomatic orthostasis																
<i>Blood Pressure: seated</i>																
<i>supine</i>																
<i>standing</i>																
<i>Weight</i>																
<i>Pulse: seated</i>																
<i>standing</i>																
Name of Examiner																
	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST
Hoehn & Yahr Stage																
% ADL Score (PD)																
% ADL (with dyskinesia)																

Fahn S, Elton R, Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease, Vol 2. Florham Park, NJ. Macmillan Health Care Information 1987, pp 153-163, 293-304