CHARACTERIZATION OF PAIN AS A NON-MOTOR SYMPTOM IN PARKINSON'S DISEASE- A CROSS SECTIONAL OBSERVATIONAL STUDY FROM A TERTIARY CARE CENTER IN SOUTH INDIA

Dr. Prabhu A S

DM NEUROLOGY THESIS

Year: 2020-2022

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND

TECHNOLOGY, TRIVANDRUM

An Institution of National Importance established by an Act of the Indian Parliament
(Act No.52 of 1980)

Dept. of Science and Technology, Govt. of India
www.sctimst.ac.in

CHARACTERIZATION OF PAIN AS A NON-MOTOR SYMPTOM IN PARKINSON'S DISEASE- A CROSS SECTIONAL OBSERVATIONAL STUDY FROM A TERTIARY CARE CENTER IN SOUTH INDIA

A THESIS SUBMITTED BY

Dr Prabhu A S

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DM NEUROLOGY

YEAR: 2020-2022

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr. Prabhu A S, hereby certify that I had personally carried out the work depicted in the thesis titled, **"CHARACTERIZATION OF PAIN AS A NON-MOTOR SYMPTOM IN PARKINSON'S DISEASE- A CROSS SECTIONAL OBSERVATIONAL STUDY FROM A TERTIARY CARE CENTER IN SOUTH INDIA"**. No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

A. S. Prabhu

Dr. Prabhu A S

Date: 08/08/2022

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH GUIDE

Name of the Guide: **Dr. Syam K**

Department: **Comprehensive Care Centre for Movement Disorders, Department of Neurology**

This is to certify that **Dr.Prabhu A S**, Department of **Neurlogy** of this institute has fulfilled the requirements prescribed for the DM degree of the Sree Chitra Thirunal Institute for Medical Sciences and Technology, Trivandrum.

The thesis entitled, "**Characterisation of pain as a non-motor symptom in Parkinson's disease- A cross-sectional observational study from a tertiary care center in South India** " was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma before this date.

Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

Date: 08/08/2022

Signature

Dr. Syam K

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the Co-Guide: **Dr. Divya K P**

Department: **Department of Neurology**

This is to certify that **Dr. Prabhu A S**, Department of **Neurology** of this institute has fulfilled the requirements prescribed for the DM degree of the Sree Chitra Thirunal Institute for Medical Sciences and Technology, Trivandrum.

The project work under the thesis entitled, "**Characterisation of pain as a non-motor symptom in Parkinson's disease- A cross-sectional observational study from a tertiary care center in South India",** was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma before this date.

Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

Date: 08/08/2022

Signature

Dr. Divya K P

Forwarded:

This is to certify that thesis entitled "**Characterisation of pain as a non-motor symptom in Parkinson's disease- A cross-sectional observational study from a tertiary care center in South India"** a bonafide research work done by **Dr Prabhu A S**, senior resident, in Department of Neurology in partial fulfillment of the requirement for DM Neurology degree.

Date: 08/08/2022

Trivandrum.

Sylaja P.N.

Dr Sylaja P N

Professor and Head,

Department of Neurology, SCTIMST

ACKNOWLEDGEMENTS

I take this opportunity to express my sincere gratitude to **Dr. Syam K**, Professor of Neurology, SCTIMST, my guide for the study, for his expert guidance, constant review, kind help and keen interest at each and every step of the study.

I am extremely thankful to **Dr. Divya KP**, Assistant Professor, Department of Neurology for her valuable input and assistance to the study.

I am grateful to **Mr. Gangadhara Sarma**, Clinical Psychologist, Department of Neurology, SCTIMST, for his assistance in patient screening and recruitment.

I am thankful to the entire faculty of the Department of Neurology, nursing staff, social workers in Comprehensive Care Centre for Movement Disorders and my colleagues for their valuable input and assistance to the study. I am extremely grateful to my family and friends for their overwhelming support and encouragement.

I extend my gratitude to all my patients and their primary caregivers who participated in this study, without whose cooperation this study would not have been possible.

Dr. Prabhu A S

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	PD	Parkinson's disease
2	KPPS	King's Parkinson's disease Pain Scale
3	NMSS	Non-Motor Symptoms Scale for Parkinson's disease
4	MOCA	Montreal Cognitive Assessment
5	BDI	Beck's depression inventory
6	MDS-UPDRS	The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale
7	NMS	Non motor symptoms
8	PDQ	Parkinson's Disease Questionnaire
9	VAS	Visual Analogue Scale
10	QoL	Quality of Life
11	MMSE	Mini-Mental State Examination
12	REM	Rapid eye movement
13	COMT	Catachol-o-methyl-transferase
14	STN	Subthalamic nucleus
15	DBS	Deep brain stimulation
16	LEDD	Levodopa equivalent daily dose

SYNOPSIS

BACKGROUND:

Pain is an important non-motor symptom in PD. As patients predominantly present with motor symptoms, non-motor symptoms especially pain are underdiagnosed. There is lack of validated scales to assess pain specific to PD. KPPS is the only validated scale to characterise pain in PD**.**

OBJECTIVES:

(1) Translation of KPPS to Malayalam for use in Keralite patients

(2) Assessment of the characteristics**,** frequency, and severity of pain in consecutive patients with PD, attending the clinical services of the Comprehensive Care Centre for Movement Disorders, SCTIMST using the Malayalam version of KPPS

(3) Determination of demographic and clinical characteristics associated with pain in patients with PD

(4) Comparison of the pain profile reported by PD patients and age and gender matched healthy volunteers

HYPOTHESIS:

(1) Pain occurs as a non-motor symptom in Indian patients with PD and can be quantified and characterized using the KPPS

(2) Pain could be reported by age matched healthy volunteers; the frequency, profile and severity of these are distinct from those with PD.

METHODS:

KPPS was translated into Malayalam after taking necessary permissions and following standard guidelines and applied on 50 consecutive patients with PD visiting Movement disorder clinic of SCTIMST. These patients underwent a second questionnaire assessment two weeks later and the results obtained was compared with that of the initial done during the clinic visit to assess test-retest reliability. Subsequently, 100 more consecutive patients and 150 healthy volunteers were enrolled in the study. Demographic and clinical data like age, sex, age at onset of disease, duration of disease and drug history were noted. Drugs consumed by patients were converted to LEDD and documented. Non-motor dysfunction, cognitive dysfunction and intensity of depression in PD were assessed using Non-Motor Symptoms Scale for Parkinson's disease (NMSS), Montreal Cognitive Assessment (MoCA) and Beck's depression inventory (BDI) respectively. Motor symptoms and severity of PD was established with The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Necessary permissions were taken from the International Parkinson and Movement Disorder Society, for using NMSS and MDS-UPDRS for this study.

RESULTS:

The test-retest reliability of the Malayalam version of KPSS was found to be good, in the initial 50 patients. The mean age of the subjects with PD (N=150) was 58.1 years (±10.1) (Range :33–81 years). The male: female ratio was 2:1. Healthy volunteers were age and sex matched with the cases. Mean duration of disease for the patients was 7.7 (±4.5). 138 patients (92%) reported pain which is higher than the prevalence of pain in any of the previously reported studies. Mean KPPS score for

cases was 17.6 (±20.4). As expected, healthy controls reported much lesser pain- mean score was 3.8 (± 6.3). The difference was highly significant statistically (Independent-samples t-test; p<0.0001). Musculoskeletal was the most prevalent pain type in patients reported by 110 patients (73%), followed by nocturnal pain (N=99, 66%), fluctuation-related pain (N=96, 64%), chronic pain (N=60,40%), discoloration/ oedema/ swelling-related pain (N= 56; 37.3%), radicular pains (N=43,29%) and orofacial pain (N=36, 24%%). Mean LEDD of patients was 920.4 (± 563.5 mg). We did not find any statistically significant association with age at onset (r=-0.05, p=0.516) and disease duration (r=0.08, p=0.312). LEDD, however showed weak association with KPPS (r = 0.214, p=0.008).

KPPS scores correlated positively with NMSS (r= 0.66; p<0.001) and BDI (r= 0.24; p=0.004) scores. Positive correlation was also noted between KPPS and MDS-UPDRS scores (r= 0.47; p<0.001) indicating that pain correlates with increasing motor severity. KPPS had a weak negative association with MOCA scores. (r= -0.198; p=0.015)

CONCLUSION:

The Malayalam version of KPPS is a valid tool to assess pain in PD in South-Indian Malayalam-Speaking patients. We found a high prevalence of pain as a non-motor symptom in PD, which is often under-recognised. Musculoskeletal pain was the most common type of pain. Pain as a non-motor symptom, was more in those who were having higher burden of other non-motor symptoms and depression. KPPS scores positively correlated with MDS-UPDRS indicating that pain increased in patients as disease severity increased. Our findings should prompt treating clinicians to actively

look for this symptom in patients with PD and modify treatment strategies accordingly, as pain could be an important determinant of the quality of life of the patients.

INTRODUCTION

1. INTRODUCTION

PD is a progressive, chronic, neurodegenerative disease. The clinical picture of PD, particularly in its early clinical course, is characterised by disturbances of motor function, manifesting as rigidity, bradykinesia, postural instability, and rest tremor. However, PD has lot of non-motor manifestations[1] too, including those affecting cognition, behaviour, autonomic functions, sleep, sensory functions and importantly, pain [2,3].

PD is traditionally considered as a predominantly motor disorder (causing abnormalities of voluntary movement). The 'non-motor' manifestations are being increasingly recognized over the past two decades. Pain is an important nonmotor symptom in PD. Pain in PD is often overlooked, as treating Physicians primarily look at PD as a motor disease. Pain in PD is highly heterogenous in clinical presentation and probably, in underlying pathophysiology also. Different types of pain have been described with variable frequency. Charcot himself, in his descriptions long ago, had noted a relationship between PD and pain.[4,5]

Pain is a symptom which could contribute to severe disability[1]. Adequate pain treatment may improve quality of life[6]. As the disease progresses, non-motor symptoms (NMS) represent considerable illness burden and the NMS may dominate the clinical picture in very advanced stages of PD in some patients.

The prevalence of pain in PD patients reported in previous studies varies between 40% to 85%[7]. Pain can present as a symptom at any time during the course

of disease and may even be the presenting symptom before the diagnosis, similar to some of the other NMS like depression, sleep disturbances or constipation.[8]

The main hindrance in the systematic assessment of pain as a non-motor manifestation of PD, until recently, was the unavailability of a disease specific assessment scale. Previous attempts to explore pain in PD from the Indian subcontinent used the VAS[9], for this reason.

Chaudhuri et al[10] from King's College, London have devised and validated the KPPS, which is a disease specific instrument to assess and quantify the different types of pain which patients with PD experience. Behari et al[11] (2020) used a Hindi version of KPPS in North Indian patients and evaluated the severity, frequency and types of pain in PD. They tested the association of pain in PD patients as assessed by KPPS with severity and stage of PD, QoL, duration of PD, gender and presence of anxiety and depression. A study by Agrawal et al[12] published in 2021 (after our study started) assessed the predictors of pain and investigated its impact on QoL among Indian PD patients. This study used KPPS and PDQ-8 to evaluate pain and QoL, respectively.

There is paucity of data on the characteristics and determinants of pain in PD patients in the South Indian population, and validated assessment scales for use in these patients are lacking. As part of this study, we translated the validated KPPS to Malayalam for use in Malayalam-speaking South Indian patients. We also assessed the frequency, characteristics, and determinants of pain as a non-motor manifestation in our cohort of South-Indian patients. Assessment of pain severity, characteristics and determinants in our population can aid in determining whether the studies done elsewhere on non-motor aspects of PD can be extrapolated to our population. We hope

that the information generated on the prevalence and characteristics of pain will prompt the practicing clinicians to actively look into this disabling but often neglected aspect of PD and also aid future research in this perspective.

OBJECTIVES OF THE STUDY

2. AIMS AND OBJECTIVES

Hypothesis: (1) Pain occurs as a non-motor symptom in South Indian patients with PD and can be quantified and characterized using KPPS translated to native language (2) Pain could be reported by age and gender matched healthy volunteers; the frequency, profile and severity of these are distinct from those with PD.

AIMS:

(1) To have a Malayalam version of KPPS, to facilitate assessment of pain in Malayalam-speaking South Indian patients with PD

(2) To determine the frequency, severity, characteristics and determinants of pain in South Indian patients with PD.

(3) To determine how the pain as a non-motor symptom of PD is different from the pain reported by general population without PD

OBJECTIVES:

(1) To create a Malayalam version of KPPS, by translating the validated English version, following all the scientific guidelines and with due permissions from its copyright holders

(2) To study the frequency, characteristics and severity of pain in consecutive patients with PD, attending the clinical services of the Comprehensive Care Center for Movement Disorders, SCTIMST using the Malayalam version KPPS and to explore

its relation with other non-motor symptoms as assessed by NMSS, BDI and MoCA and motor dysfunction, assessed by MDS-UPDRS.

(3) Comparison of the pain profile reported by PD patients and age and gender matched healthy volunteers.

REVIEW OF LITERATURE

3. REVIEW OF LITERATURE

The reported prevalence of pain in PD in Western studies varies between 24 to 85%[12-15]. Musculoskeletal pain is the most frequent pain (40-75%)[16,17], followed by radicular pain (5-20%), as per Western data. Patients with PD have been shown to have significantly higher pain severity scores than age- and gender-matched controls. About 50% of PD patients report moderate to severe pain during the course of the disease. An Indian study which used visual analogue scale to examine pain, reported the prevalence of pain in PD as 54.8%[9].

MECHANISM OF PAIN IN PD:

Pain modulation is brought about by dopamine at different levels[19]. Neuroimaging studies that have been done in humans showed that pain modulation involves striatal dopamine D2 receptors[20]. This suggests that abnormal basal ganglia function in PD could lead on to defective modulation and perception of pain. Several mechanisms have been proposed, including direct increase of nociceptive signal propagation or and indirect mechanisms like changes in affective and cognitive processes involved in pain perception. The indirect mechanisms alter the manner how patients expect, experience and interpret nociceptive signals and pain.

Pain in PD has also been associated with motor fluctuations. The role of dopamine in pain signalling is complex. Pain relief activates reward mechanisms of the brain, mediated by elevated dopamine in nucleus accumbens and related regions. Reciprocity with higher brain regions such as the anterior cingulate cortex and dopaminergic transmission therein are necessary for the relief of pain aversiveness.

Certain forms of pain in PD have been demonstrated to be reduced by dopaminergic treatments, fluctuation-related pain in PD is probably mediated by dopamine deficiency. A positive signal for Opicapone was observed on the NMSS miscellaneous domain, which encompasses pain, in both the OPTIPARK study and the BIPARK II trial.[21]

Pain mechanisms in PD can be classified into central and peripheral mechanisms. Central causes consist of a lower pain threshold, changes in pain processing, and motor/non-motor fluctuations. Thompson et al. found pain hypersensitivity in patients with PD[22]. Peripheral causes consist of Levodopa-induced Vitamin B12 deficiency and altered inflammatory mechanisms.

TYPES OF PAIN IN PD:

There are different classification systems of pain for PD.

According to Deuschl and Wassner[23], pain of PD can be divided into nociceptive (musculoskeletal, visceral, cutaneous) and neuropathic (peripheral, central) types. Musculoskeletal pain is a type of nociceptive pain that originates from abnormal posture, rigidity, and akinesia and painful dystonia occurring in those with motor fluctuations. Early morning dystonia, manifesting as focal dystonia with plantar flexion and foot inversion is the most typical painful dystonia. Visceral pain frequently accompanies constipation. Painful anismus can result from dystonic contractions of the anal sphincter.

Pain may be peripheral or central neuropathic pain. Neuropathic pain in PD consists of radicular pain and central Parkinson's pain. Radicular pain has a higher

prevalence in patients with PD than in the general population. It manifests due to festination, kyphosis and dystonia causing lumbar discal structure damage. Central Parkinson's pain is relatively rare (4–10 % of patients). It majorly affects the body side with predominant motor symptoms. It is described as a burning, cramping sensation usually.

Chaudhuri and Schapira[1] classified pain into musculoskeletal, PD-related chronic pain, fluctuation-related, nocturnal, coat-hanger, orofacial, peripheral limb and abdominal pain

Ford's pain classification[24] (2010) is the most-cited one. It classifies pain in PD to five types based on their origin and the treatment approach. The five different types are musculoskeletal pain, radicular-neuropathic pain, dystonic pain, central neuropathic pain and akathisia[24]. Neuropathic central pain is a somewhat disease-specific symptom in PD but also described in stroke[25] and multiple sclerosis.[26]

Musculoskeletal pain:

Musculoskeletal pain is the most common type of pain in patients[16] with PD with a prevalence from 40% to 75%[27-30]. This prevalence rate is higher in PD patients than the general population (reported to be 10%–25%). Musculoskeletal pain is generally associated with abnormal postures and deformities, such as camptocormia, kyphoscoliosis, dropped head syndrome, Pisa syndrome, joint changes due to chronic dystonic posturing and bone mineralization disorders and joint disorders, including frozen shoulder[31]. Musculoskeletal pain can be of different types such as spinal paravertebral pain, joint pain, and lower back pain.[32]

Patients with PD have an increased thoracic kyphosis and decreased truncal mobility[33]. Frozen shoulder results from peri-arthritis or adhesive capsulitis, with a spontaneous onset of pain and a gradual restriction in the range of motion. It can appear within 1 or 2 years before the onset of motor features. It can hence be viewed as a pre-motor feature of PD. More than half of the patients with PD have lower back pain[34]. Muscular imbalances resulting from the movement disorder as well as skeletal deterioration can both contribute to lower back discomfort.

Radicular pain:

The second next most common type is radicular pain[35]. The prevalence of radicular pain in patients with PD ranges from 5% to 20%. Pain manifests with numbness or weakness in the nerve root territory. The increased occurrence of radicular pains in PD is caused by truncal abnormalities predisposing to cervical or lumbar radiculopathies, which develop during the disease course.

Dystonic pain:

Painful dystonia develops in around 1/3rd of patients with PD[36] that receive long-term Levodopa treatments. Prevalence of dystonia-related pain ranges from 8% to 50% in patients with PD. Foot dystonia is very painful and causes difficulties in walking[37]. It ranges from simple forms, such as inversion or hallux extension, to complex forms, like combinations of inversion, plantar and toe flexion or extension. This typically occurs in the morning, before the first dose of Levodopa. It can occur even during medicated periods.

Polyneuropathy and neuropathic pain:

The prevalence of peripheral neuropathy in patients with PD ranges from 37.8 to 55%[38,39]. PD patients have an increased prevalence of symmetrical neuropathy, especially in sensory axons[40]. The risk of polyneuropathy is found to be higher in patients taking high doses of Levodopa. Kaur et al. described a patient who developed acute neuropathic pain related to a treatment of Levodopa-carbidopa intestinal gel (LCIG) infusion with pre-existing polyneuropathy[1]. Vitamin B12 replacement improved LCIG-related polyneuropathy.[42,43]

Orofacial pain:

Orofacial pain is an anatomical classification of pain in patients with PD. Orofacial pain includes pain when chewing, nocturnal teeth grinding pain, and burning mouth syndrome. Pain when chewing is thought to be secondary to temporomandibular joint disorders attributed to auriculotemporal nerve pathology in PD[44]. There is a higher rate of bruxism in patients with PD. Burning mouth syndrome is a painful, intraoral burning sensation, without physical or laboratory correlates. Its prevalence in PD varies from 4% to 24%.

The KPPS evaluates seven domains corresponding to the diverse forms of pain identified in PD. The high frequency of these pain disorders in the general population makes it hard to establish whether pain is more frequent among people with PD than among age-matched controls. KPPS has already been used as a reliable tool available in English language to assess various types of PD-related pain. Recently, validated versions in German, French, Spanish, Turkish, Hindi, Persian, and Bulgarian languages have been published[45.] According to KPPS developers, more studies are

required in other languages to generalize the results better and to make optimal use of this scale.

RISK FACTORS FOR PAIN IN PD:

Clinical risk factors:

Clinical risk factors for pain in PD include the female sex, an early age of onset, motor complications, a long disease duration, depressive symptoms, and comorbidities (e.g., diabetes mellitus, osteoporosis, rheumatic disease, degenerative joint disease, arthritis, and disc herniation). Among these clinical risk factors, the evidence of age in pain of PD is controversial and the results are conflicting. Studies have shown that dystonia-related pain was observed at earlier ages.

Depression and other non-motor symptoms in PD:

Pain is closely related to other non-motor symptoms, including depression, fatigue, daytime sleepiness, and sleep disorders. Patients with PD that had depressive symptoms had significantly higher pain interference and pain severity scores than controls who did not have depressive symptoms[46].

Cognitive dysfunction, evaluated with the MMSE, did not correlate with duration of pain in PD[17]. In another study, the non-motor symptoms scale showed a correlation between pain and attention/memory[18].

Other non-motor symptoms have shown similar associations. Patients with PD who experienced poor sleep quality displayed higher pain severity scores and higher severity for depression and anxiety. PD patients with pain had longer sleep latencies, shorter total sleep times, less time in the REM stage of sleep, more wakefulness after

sleep onset, and poor sleep efficiency. Polysomnography showed that those with pain showed more light sleep (N1) and less deep sleep (N2 and slow-wave sleep) than those without pain[47]. Restless leg syndrome was not significantly correlated with depression, anxiety, or pain.

SCALES USED FOR PAIN ASSESSMENT IN PREVIOUS STUDIES:

Brief Pain Inventory (BPI)[48]:

This is a simple and short, self-reported questionnaire using a 10-point Likert scale as a response alternative and assesses pain intensity and interference with functions. It employs pain severity index, which is calculated by adding the scores on the pain severity items (worst pain, least pain, pain now, average pain in the last 24 hours and in the last week)

This scale evaluates pain intensity and interference with activities of daily living, pain localization and relief from treatments. Time to complete the scale is 5 to 10 minutes

Medical Outcomes Study 36-Item Short Form:

Medical Outcomes Study 36-Item Short Form (SF-36) is another scale used. The responses are added and transformed to a 0–100 scale (0 = worst pain, 100 = no pain)[49]

KPPS:[45]

This is the first internationally validated disease- specific scale to evaluate the burden of pain in PD. It measures different domains of pain in patients with PD. This

is a rater-interview-based scale and assesses localization, intensity, and frequency of pain and its relationships with motor fluctuations. The scale has 14 items grouped into seven domains..

1. Musculoskeletal pain (item 1)
2. Chronic pain (items 2 and 3)
3. Fluctuation-related pain (items 4–6)
4. Nocturnal pain (items 7 and 8)
5. Orofacial pain (items 9–11)
6. Discoloration, Oedema/Swelling- related pain (items 12 and 13) and
7. Radicular pain (item 14).

Each item is scored by severity (0 to 3) multiplied by frequency (0 to 4) resulting in a range from 0 to 12 for each item and a possible total score of 0- 168. A cut-off point greater than 17 (sensitivity = 90.97 and specificity = 91.11) and 68 (sensitivity = 70.97 and specificity = 99.09) respectively have been used to distinguish mild pain from moderate pain, and moderate pain from severe pain.

11-Point Numeric Rating Scale (NRS) and 100-mm VAS:

Both scales measure of pain intensity. The VAS is a 100- mm line with no pain at one end and worst pain at another[51]. The patient is asked to mark their pain level. The NRS is similar and consists of 11 points (no pain to maximal pain). Patients are asked to indicate which number best describes his or her pain intensity. Both scales

take less than 30 seconds. Some PD patients may have difficulties in drawing crosses in VAS because of motor symptoms but this is yet to be formally tested.

Leeds Assessment of Neuropathic Symptoms and Signs:

It has two parts and can be used to discriminate between nociceptive and neuropathic pain. The first part is a questionnaire with five self-administered questions which includes unpleasant sensations, sensitivity to touch, skin appearance, pain feelings, and skin temperature. The second part is a sensory testing consisting of two items (altered pinprick threshold and allodynia) conducted by a physician. This is totalled to a maximum of 24 points; the patient is said to have neuropathic pain when values ≥12. It can be completed in 5 to 10 minutes[52]. It has not been validated in PD.

McGill Pain Questionnaire Long Form[53] and short form:

This self-administered questionnaire can be used to characterize the dimensions of pain and is comprised of four parts. The first part includes a body map which is used for localizing pain. Patients are asked to disclose pain-related feelings in the second part, by choosing the appropriate words. The third part evaluates changes over time and the fourth part characterizes pain intensity. It takes up to 30 minutes to complete. Some patients may have difficulty comprehending the terminologies. The shortened version of the McGill Pain Questionnaire is comprised of 15 words describing different aspects of pain. Patients indicate pain intensity on a scale of 0 to 3. It takes 5 to 10 minutes to complete this scale but has the same disadvantage as the long version.

Utility of KPPS:

The KPPS is the most "recommended" scale for the assessment of pain intensity in PD and is being used increasingly now[54]. It has been used outside Western population, too and has been translated to several languages. Hirsi et al[55] used KPPS and reported prevalence of pain in PD patients in an outpatient clinic in Ethiopia to be 84%. An Indian study in 2020 used a Hindi translated version of KPPS and evaluated correlation between KPPS scores and QoL and depression[11]. Another recent Indian study conducted in New Delhi[12] used the original English version of KPPS as a measure to assess and define characteristics of pain in PD patients.

Martinez-Martin et al found that most of the pain categories covered by KPPS have an effect on health-related quality of life, with the exception of musculoskeletal pain and pain related to periodic leg movements/restless legs syndrome[56].

Patients with PD who displayed depressive symptoms had significantly higher pain severity and pain interference scores than age and gender matched healthy controls without depressive symptoms[46].

The administration of Levodopa has been shown to markedly raise pain threshold in PD patients but not in healthy subjects[57]. Nonspecific pain may be more responsive to Levodopa, compared to radicular, neuropathic, or akathisia-related pain. Qureshi et al. performed a meta-analysis on pain treatments in PD and found that the greatest reductions in pain were found with the anti-PD medication safinamide, followed by cannabinoids, opioids, and COMT inhibitors[58]. Bilateral STN-DBS improved pain, particularly pain related to dystonia, in 50% of patients with PD after a mean follow-up period of 5 years. Significant improvements in KPPS total score,

KPPS domain 3 (items 4–6, fluctuation related pain), KPPS item 5 (region-specific "off" dystonia), and UPDRS IV were observed after treatment with safinamide, while maintaining stable dopaminergic medication[59]

Pain is a major non-motor symptom in PD patients. Although there are many studies on pain in PD, only few studies had used the recommended KPPS. There is one Indian study on pain in PD which used the VAS[9]. However, the VAS has not been fully validated for use in PD. There are very few studies from India that have used the validated KPPS as a measure of pain. Hence, we decided to better define the characteristics, frequency, severity and determinants of pain in our cohort of South Indian patients with PD using the internationally validated KPPS.

METHODOLOGY

4. MATERIALS AND METHODS

The study was carried out in 2 phases in the Movement Disorders Clinic of SCTIMST Trivandrum.

Phase I: The copy-right holders of KPPS were contacted and formal permissions were obtained for translation of KPPS and its use in this study. The KPPS questionnaire was translated to Malayalam by a team of bi-lingual experts who were well experienced in such tasks. The Malayalam version of the KPPS was administered to 20 patients with PD, attending the Movement Disorders Clinic of the Institute. These patients underwent a detailed clinical interview by two other investigators – Co-Principal Investigator 1 / Co-Investigator 1(who are Movement Disorder Specialists) for a cognitive debriefing and the translated version was modified to ensure accuracy of the information captured, accordingly. Back translation of the Malayalam version was done and the back translated version was compared with the original and discussed among the team of investigators and consensus was obtained. The final back-translated version was judged satisfactory. Subsequently, 50 patients were interviewed using Malayalam version of KPPS. The patients also underwent a comprehensive clinical assessment including history, neurological examination and assessment of motor and non-motor features of PD using the MDS-UPDRS and the NMSS. A screening Neuropsychological assessment was also done, consisting of screening for cognitive functions (MoCA) and depression (BDI). These patients underwent a second KPPS questionnaire assessment (telephonic interview by Principal Investigator / Co-Investigator 2) two weeks later and the results obtained were compared with that of the initial done during the clinic visit to assess test-retest reliability.

Phase 2: Estimation of the prevalence and determinants of pain in patients with PD

In addition to the 50 PD patients recruited in Phase 1, 100 more consecutive patients with PD were recruited in phase 2 and assessed using the KPPS. All the other assessment scales applied for patients in phase 1, were done for these patients too. The treatment history was collected, including the dose and duration of Levodopa and the ongoing LEDD. Pain similar to that reported by patients with PD have been shown to occur in elderly without PD also at a lower frequency and intensity (these could be non-specific or related to musculoskeletal co-morbidities), and therefore, age and gender matched healthy volunteer group was also investigated.

Consecutive patients from the Movement Disorders Clinic, who satisfy the eligibility criteria, were included. Healthy volunteers who were age and sex matched with the patients were recruited from among the friends and visitors of patients attending the Neurology Outpatient Clinics / admitted in Neurology Wards. The healthy volunteers were recruited through a call notification, approved by the Institutional Ethics Committee, displayed in these places. The guidelines of the ethics committee for recruitment of healthy volunteers were followed. All healthy volunteers were examined by the investigators. Incidental medical diseases were identified in a few volunteers and they were provided guidance for its management.

Following were the eligibility criteria:

Patients with PD:

Inclusion Criteria:

(1) Diagnosis of PD using the United Kingdom Parkinson's Disease Brain Bank criteria

(2) Age more than 30 years

Exclusion criteria:

(1) PD dementia (PDD), causing impairment of daily activities

(2) Active neuropsychiatric disturbances which are likely to interfere with the patients' ability to give informed consent / co-operate with the assessments

(3) Significant morbidity from co-existing medical conditions which are likely to interfere with the assessments, in the judgment of investigators

(4) History of undergoing Deep Brain Stimulation or any other functional neurosurgical procedure for controlling the symptoms of PD.

Healthy Volunteers:

Inclusion Criteria:

(1) Age and sex matched to patients with PD

(2) No clinical evidence for PD or any other neurological disorder Exclusion criteria: (1) Dementia (2) Active neuropsychiatric disturbances which are likely to interfere with the patients' ability to give informed consent / co-operate with the assessments

(3) Significant morbidity from co-existing medical conditions which are likely to interfere with the assessments, in the judgment of investigators.

STATISTICAL METHODS:

The data from KPPS was analysed to determine the overall frequency and severity of pain among patients with PD and the different types of pain. This was compared with the data from healthy volunteers. Numerical variables were summarized as means and standard deviations and categorical variables were summarized into proportions. Students t test was used to compare the KPPS scores between the two groups (PD and Healthy Volunteers). The correlation between KPPS scores and the clinical characteristics like age, age of onset of PD, duration of motor symptoms of PD, LEDD etc was assessed using Pearson's correlation co-efficient.

RESULTS

5. RESULTS

150 PD patients (50 recruited in phase 1 and 100 in phase 2) and 150 age and sex matched healthy volunteers were recruited. Malayalam version of KPPS was applied on these patients and healthy volunteers

DEMOGRAPHIC AND CLINICAL FEATURES:

AGE DISTRIBUTION:

Table 1.1 Age distribution of Healthy Volunteers (n = 150) and Patients with PD (n = 150)

	Healthy volunteers	**PD patient group**
Mean	55.93	58.11
Median	55	58
Standard deviation	8.2	10.08
Range	32-82	33-81

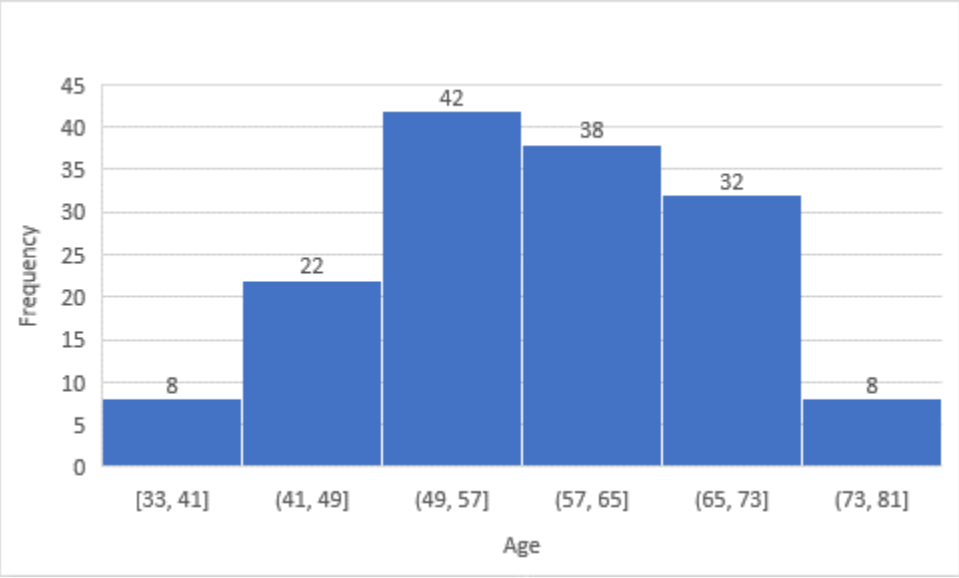


Figure 1. Age distribution of study group

The range of age distribution in the PD group was 33-81. The distribution range in the healthy volunteer group was 32 – 82. The mean age of patients with PD was 58.1(±10.8) vs 55.9(±8) in the healthy volunteer group. The age distribution in the study group and the healthy volunteer group was similar.

GENDER DISTRIBUTION:

The study group and healthy volunteers' group were sex matched. There was a total of 48 females (32%) and 102 males (68%) in both the groups. There were equal number of males and females in the PD patient group and healthy volunteer group.

AGE AT ONSET:

The mean age at onset was 50.5 (±10.9). It ranged from a minimum of 23 to a maximum of 77.

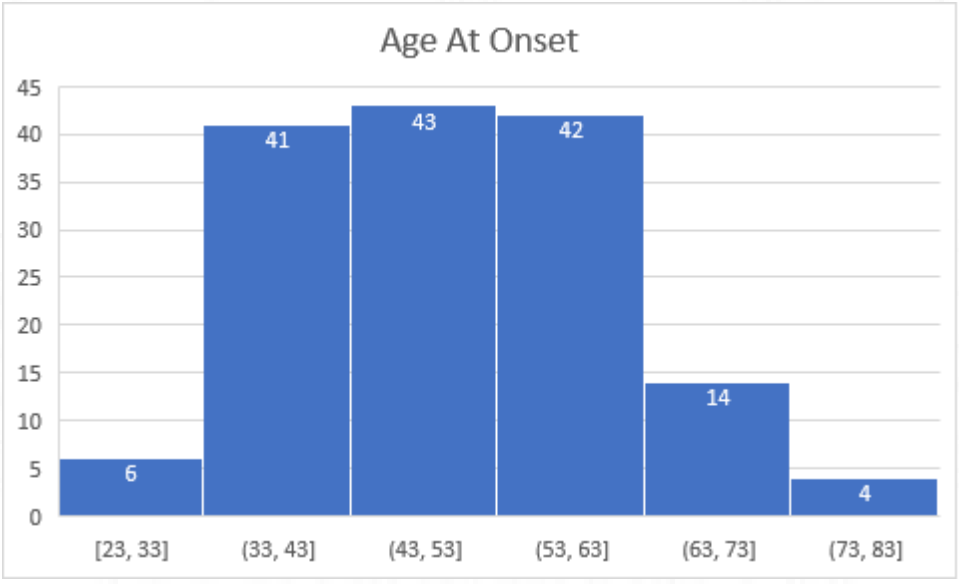


Figure 2. Distribution of age at onset of disease

Table 1.2: Correlation between the Age at onset and the KPSS score in patients with PD (n=150):

		Total KPSS Score	Age at Onset
Total KPSS Score	Pearson Correlation Sig(2-tailed) N	1 150	-.053 .516 150
Age at Onset	Pearson Correlation Sig(2-tailed) N	-.053 .516 150	1 150

Negative correlation was observed in our study between the KPSS score and the age at onset which was not statistically significant. (r=-0.05, p=0.516)

DURATION OF DISEASE:

The mean duration of disease in the study population was 7.7 years (±4.5). It ranged from 1-25 years.

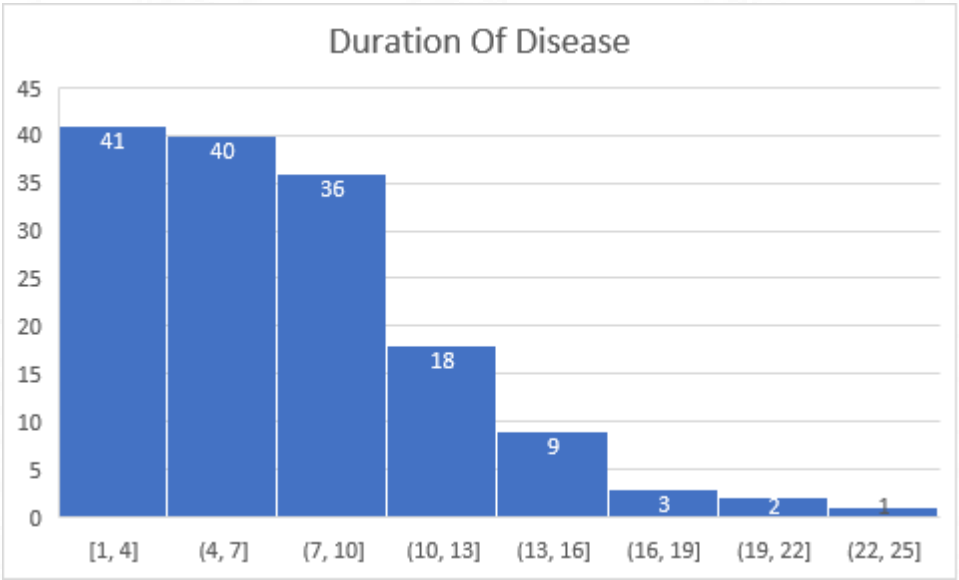


Figure 3. Distribution of duration of disease

41 patients (27%) had less than 4 years of disease duration. 40 patients had between 4-7 years of disease. Number of patients with 10 or more years of PD was 33 (22%).

Table 1.3: Correlation between the Duration of the disease and the KPSS score in study participants (Patients with PD) (n=150):

		Total KPSS Score	Duration of the Disease
Total KPSS Score	Pearson Correlation Sig(2-tailed) N	1 150	.083 .312 150
Duration of the disease	Pearson Correlation Sig(2-tailed) N	.083 .312 150	1 150

There was a weak positive association observed between duration of the disease and the KPSS score (r=0.08, p=0.312) which was not statistically significant.

LEDD:

Treatment history of patients was collected and analysed. All drug dosages were converted into equivalent doses of Levodopa.[60]

It ranged from a minimum of Zero (The patients were not on Levodopa or other dopaminergic medications and received only anticholinergics) to a maximum of 3214 mg. Mean LEDD was 920.38 mg±563.5 mg.

Our study showed a weak association between LEDD and the total KPSS. (r = 0.214, p=0.008)

KPPS SCORE:

KPPS was initially checked for 50 patients and retested after 2 weeks.

Table 4: KPPS scores of study participants (Patients with PD) (n=50) at recruitment and after 2 weeks

S,No	Age	Gender	Initial KPPS score	KPPS score after 2 weeks
1	58	Female	26	24
2	64	Female	0	1
3	56	Female	35	34
4	65	Female	18	19
5	41	Female	39	40
6	50	Female	26	25
7	70	Male	18	19
8	66	Female	13	15
9	54	Female	1	2
10	61	Female	5	2
11	59	Female	1	3
12	53	Female	46	45
13	61	Male	64	65
14	65	Male	30	28
15	63	Male	49	44
16	56	Male	26	29
17	77	Male	4	5
18	50	Female	28	29
19	65	Female	51	50
20	81	Female	23	22
21	63	Female	1	3
22	41	Female	52	50
23	63	Female	13	14
24	41	Female	0	1
25	45	Female	25	25
26	55	Female	24	24
27	46	Female	11	11
28	45	Female	8	9
29	54	Male	8	8
30	69	Male	5	5
31	77	Male	50	51
32	40	Male	76	77

33	50	Male	32	33
34	55	Male	8	7
35	81	Male	54	55
36	53	Female	12	10
37	54	Female	9	8
38	57	Female	6	6
39	51	Female	1	1
40	57	Female	1	2
41	53	Female	0	0
42	46	Female	1	1
43	58	Female	3	3
44	41	Female	1	1
45	51	Female	2	2
46	51	Female	3	3
47	42	Male	0	0
48	41	Female	2	2
49	47	Female	2	2
50	53	Female	9	8

Table 1.5. Test-retest reliability of KPPS

Paired Samples Statistics		Mean	Std. Deviation	P-Value	Confidence interval
Pair 1	KPPS score at the start of the study	18.44	19.7	0.920	- 0.41 to 0.37
	KPPS of 50 patients recruited in Phase 1 re-checked 2 weeks later	18.46	19.5		

Test-retest reliability of the Malayalam version of KPPS was checked in the 50 patients who were recruited in phase 1. There was a very strong positive correlation by paired-t-test between KPPS score in those study participants in whom it was re-checked. The Malayalam KPPS was found to have excellent test-retest reliability

Table 1.6. Distribution of study participants – Patients with PD (n=150) and healthy volunteers (n=150) according to their KPPS total score

	Healthy volunteers	**PD patient group**
Mean	3.84	17.55
Median	1	10
Standard deviation	6.3	20.3
Range	0-33	0-105

KPPS ranges from 0-168. Of the 150 patients in the study group 138 patients (92%) had pain. The mean score of KPPS in the study group was 17.55±20.3. It ranged from a minimum of 0 to a maximum of 105. Only 12 patients of the 150 patients in the study group did not experience pain.

The mean KPPS Score in the healthy volunteers' group was 3.8±6.3. Of the 150 healthy volunteers, 93 volunteers had pain (62%). The KPPS score ranged from a minimum of 0 to maximum of 33 in the healthy volunteers group

The difference in mean between the study participants is statistically significant ($P < 0.001$) according to the independent T-test

Thus, the patients with PD had more pain than the healthy volunteers' group according to KPPS scale score.

Table 1.7. Comparison of individual domains of KPPS in Patients with PD (n=150) and Healthy volunteers (n=150)

KPPS domains	Group	Mean	Std. Deviation	Mean Difference	P-value
Domain 1	Healthy Volunteers	2.55	3.44	- 0.14	0.710
	PD patient group	2.69	3.06		
Domain 2	Healthy Volunteers	.15	.61	-2.05	< 0.001
	PD patient group	2.17	4.39		
Domain 3	Healthy Volunteers	.00	.00	-5.41	< 0.001
	PD patient group	5.41	7.51		
Domain 4	Healthy Volunteers	.53	1.4	-3.81	< 0.001
	PD patient group	4.34	5.76		
Domain 5	Healthy Volunteers	.00	.00	- 0.79	< 0.001
	PD patient group	.79	2.05		
Domain 6	Healthy Volunteers	.51	1.22	- 0.87	0.001
	PD patient group	1.38	2.95		
Domain 7	Healthy Volunteers	.11	.43	- 0.67	< 0.001
	PD patient group	.78	1.94		

All the KPPS domains except domain 1, there was a statistically significant association between study group and the healthy volunteer group.

The most frequent type of pain in the study group was musculoskeletal pain – domain 1 of KPPS. Of the 150 study participants 110 patients (73%) had musculoskeletal pain.

The second most common type of pain was Nocturnal pain experienced by 99 participants (66%). The third most common type of pain was fluctuation related pain experienced by 96 patients (64%).

The least common type of pain was orofacial pain experienced only by 36 study participants (24%).

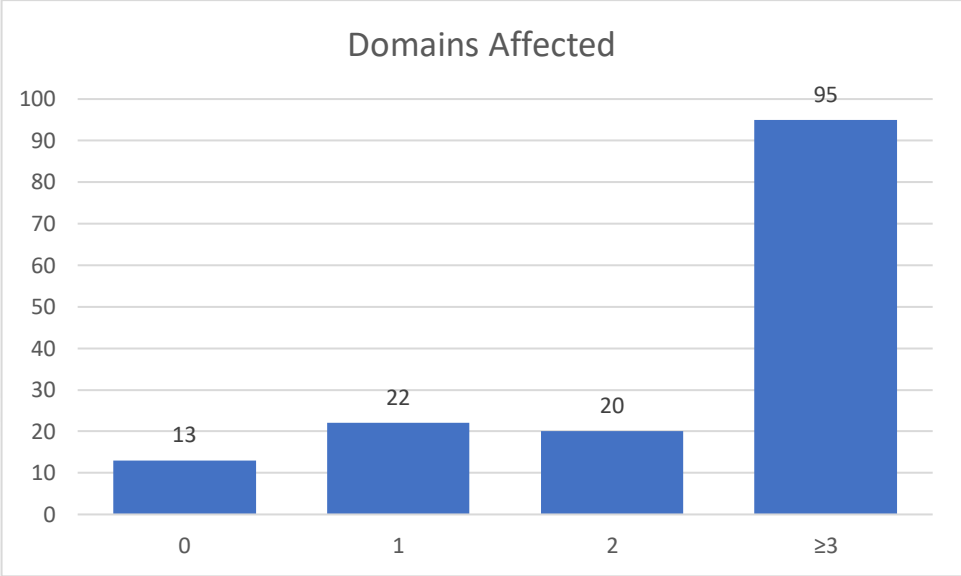


Figure 4. Distribution of number of domains of pain affecting the study group

Of the 150 study participants, 22 patients (15%) had only one type of pain while 20 patients (13%) had 2 types of pain, 95 (63%) patients had three or more types of pain. 11 patients (7%) had all 7 types of pain.

OTHER SCALES:

Table 1.8: Distribution of Scores of NMSS, MoCA and BDI in patients with PD(n=150) and Healthy volunteers (n=150)

		NMSS	MoCA	BDI
HEALTHY VOLUNTEERS	Mean	7.6	29	3.8
	Median	2	29	1
	SD	11.5	2.6	6.2
PD PATIENT GROUP	Mean	44.7	25.9	11.6
	Median	33	27	10
	SD	41.5	3.5	8.1
	P Value	<0.001	<0.001	<0.001

NMSS:

Of the 150 patients in the study group 149 patients (99%) had non motor symptoms as per NMSS scores. It ranged from a minimum of 0 to a maximum of 213. Of the 150 healthy volunteers, 57 volunteers had non motor symptoms (38%). The NMSS score ranged from a minimum of 0 to maximum of 61 in the healthy volunteers group

The difference in mean between the study participants is statistically significant ($P < 0.001$) according to the independent T-test. Thus, the PD patient group had more non-motor symptoms than the healthy volunteers group according to NMSS scale score.

MoCA:

Of the 150 patients in the study group 6 patients (4%) had moderate cognitive impairment (MOCA score 10-17). 47 patients (31%) had mild cognitive impairment (MOCA score 18-25). 97 patients (65%) did not have cognitive impairment. It ranged from a minimum of 12 to a maximum of 30. Of the 150 healthy volunteers, only one volunteer had mild cognitive impairment (MOCA score 25). The MOCA score ranged from a minimum of 25 to maximum of 30 in the healthy volunteers group.

The difference in mean between the study participants is statistically significant ($P < 0.001$) according to the independent T-test. Thus, the PD patient group had more cognitive impairment than the healthy volunteers group according to MOCA scale score.

BDI:

Of the 150 patients in the study group 73 patients had depression. 35 patients had mild mood disturbance (BDI score 11-16). 17 patients had borderline clinical depression (BDI score 17-20). 16 patients had moderate depression (BDI score 21-30). 5 patients had severe depression (BDI score 31-40). It ranged from a minimum of 0 to a maximum of 35.

11 healthy volunteers had mild mood disturbance (BDI score 11-16). 1 volunteer had borderline clinical depression (BDI score 17-20). 5 volunteers had moderate depression (BDI score 21-30). The BDI score ranged from a minimum of 0 to maximum of 30 in the healthy volunteers group

The difference in mean between the study participants is statistically significant ($P < 0.001$) according to the independent T-test

Thus, the PD patient group had more depression than the healthy volunteers' group according to Beck's Depression scale

Table 1.9. Distribution of the study participants (Patients with PD) according to MDS -UPDRS scores (n = 150)

	Domain 1	**Domain 2**	**Domain 3**	**Domain 4**	**MDS - UPDRS total score**
Mean	10.5	14.5	20.7	6.3	51.97
Median	8.50	12.00	19.00	5.00	49.00
Std. Deviation	6.9	9.7	12	5.5	25.1
Minimum	0	0	1	0	4
Maximum	35	46	61	29	130

Of the 150 patients in the study group, the mean score of MDS UPDRS was 51.97±25.1. It ranged from a minimum of 4 to a maximum of 130.

Table 1.10: Comparison of NMSS, MoCA, BDI between patients with PD(n=150) and healthy volunteers(n=150):

	Mean difference	P value
NMSS	-37.14	< 0.001
MoCA	2.94	< 0.001
BDI	-7.76	<0.001

According to independent T-test, the difference in mean between PD patient group and the healthy volunteer group was statistically significant (P < 0.001) for NMSS, MoCA and BDI scores.

Table 1.11. Correlation between KPPS score and other scales in patients with PD (n=150):

	MDS UPDRS	**NMSS**	**MoCA**	**BDI**
r Value	0.47	0.66	-0.19	0.24
P Value	<0.001	<0.001	0.015	0.004

KPPS scores patients with PD had statistically significant correlation with MDS-UPDRS (r=0.47), NMSS (r=0.66) and BDI (r=0.24). KPPS scores of patients with PD had a weak negative correlation with MoCA scores(r= -0.19).

Table 1.12. Corelation between KPPS score and individual domains of MDS-UPDRS score among PD patient group (n = 150)

		MDS domain 1	**MDS domain 2**	**MDS domain 3**	**MDS domain 4**
KPPS total score	Pearson Correlation Value	0.54	0.38	0.25	0.24
	P -Value	< 0.001	< 0.001	0.002	0.003

In patients with PD the KPPS scores and MDS-UPDRS score of all domains in the scale had statistically significant positive corelation. (r= 0.54, 0.38, 0.25, 0.24 for KPPS and MDS domains 1-4 respectively)

DISCUSSION

6. DISCUSSION

We have translated KPPS into Malayalam and shown that it has good test-retest reliability and correlates well with the total non-motor symptom burden and severity of motor deficits, indicating that it is a valid tool to assess pain in patients with PD who are Malayalam-speaking. We have also shown the characteristics of pain, its correlation with duration of disease, motor symptoms, depression, other non-motor symptoms, cognitive impairment and LEDD. It has shown that pain is a highly prevalent symptom in patients with PD and is likely under-recognized.

Among a total of 150 cases of PD, 65% of the subjects were in the 51–70-years age group. The mean age of the subjects was around 58.1 years with range of 33–81 years. Lin et al reported[61] average age of 66.24 ± 8.93 years (range: 35–85 years). In an Indian study by Agrawal et al[12], the mean age of onset of disease was 57.77 ± 12.05 years with range of 28–82 years, which is comparable to our results. In a study by Goetz et al[26], PD patients with pain were significantly younger than the patients without pain. However, age at onset did not have a statistically significant correlation with pain in our study.

Agrawal et al[12] stated that the difference among mean KPPS of different age groups, groups with different disease durations, gender groups and different LEDD wstatistically insignificant ($P > 0.05$), meaning that pain scores were not affected by the variables such as age, different LEDD, gender and disease duration. Other studies have also failed to establish any correlation between age at onset, duration of disease and pain in PD. Our study showed no statistically significant association with disease duration (r=0.083, p=0.312), age at onset (r=-0.53, p=0.516) similar to prior studies.

Mean duration of disease in the subjects was 7.7 years (±4.5). The male: female ratio was 2:1. 41 patients (27%) had less than 4 years of disease duration. 40 patients had between 4-7 years of disease. Number of patients with 10 or more years of PD was 33 (22%).

Out of 150 subjects, 138 (92%) exhibited one or more types of pain while 12 did not have any pain. The mean KPPS score of subjects in our study was 17.5 ± 20.3 with a range of 0 – 102 vs 5.23 ± 6.42 with a range of 0–27 in the study by Agrawal et al[12]. In another Indian study by Behari et al[11], the mean total KPPS score of the whole cohort was 16.02 ± 10.57. The mean KPPS in our study and this study, was similar to KPPS score of the cohort of 314 PD patients reported by Rodrıguez-Violante et al[62]. In a study by Lin et al[61], 70% of subjects experienced one or more types of pain.

There is a wide variability in the prevalence of pain in PD in the previous studies. In a study done by Bieske et al[63], the prevalence of pain was 83%. Broen et al[7], concluded that prevalence ranged from 40% to 85% in their study population. Hirsi et al[55] showed that the prevalence of pain in PD patients in their outpatient clinics was 84%. Reported prevalence in the United Kingdom is 85%[64]. Other studies however have reported pain at lower prevalence: 46% in Chicago[26], 40-69.9% in Italy[65], 61.7% in France[66], and 76% in Slovak Republic[67] In our study, of the 150 patients in the study group 138 patients (92%) had pain which is higher than the prevalence of pain in any of the previously reported studies.

Possible explanations are methodological disparities, differences in the definition of chronic pain, and recruitment bias in specialized tertiary centres. According to study by Hirsi et al[55], patients with PD report an average pain level

greater than the general population, with >50% of patients reporting one, 24% reporting two and 5% reporting three pain types. In our study, 15% had only one type of pain while 13% had 2 types of pain and 63% patients had three or more types of pain. 7% of the patients reported all 7 types of pain

Djaldetti et al[68] and Tinazzi et al[69] found that PD patients both with and without pain may have a low heat pain threshold and abnormal pain-evoked responses, which suggests that PD patients may be predisposed to developing pain.

Similar studies have reported variable prevalence of different types of pain According to Hirsi et al[55], the most common pain was musculoskeletal pain followed by pain related to difficulty turning in the bed at night. Both of these were also amongst the most bothersome according to their sub-scores. A similar study in the Slovak Republic by Valkovic et al showed that 76% of patients with PD had pain, in which 41% had musculoskeletal pain.[67]

Another study by Quinn et al[70] also reported that musculoskeletal pain was the most frequent pain (48%), followed by pain related to dystonia (26%). Similarly, patients with PD who had pain experienced more depressive symptoms[70]. In one retrospective study by Rana et al, 33% of the PD patients were initially diagnosed as having degenerative spinal disease, osteoarthritis and frozen shoulder[71].

In a previous study by Farnikova et al, it was shown that 25–64% of PD patients are thought to experience pains unrelated to this disorder[72]. Musculoskeletal was a dominant symptom in early PD stages and has been attributed the cause of 40–90% of the reported pain, as well as the most prevalent type (41–70%), followed by dystonic pain (40–48%), radicular-neuropathic pain (14–35%), central neuropathic pain (22–

36%), and other modalities pains (5.7%)[67,73]. The corresponding figures for the study by Martin et al[56] was: musculoskeletal, 84.8%; dystonic, 33.2%; radicular, 46.1%; central neuropathic, 31.5%; and oro-facial pain, 20.8%. Estimated prevalence of musculoskeletal, dystonic, radicular and oro-facial pain in our study was 73%, 64%, 29% and 24% respectively.

In our study, the individual types of pain, including musculoskeletal, chronic, fluctuation-related, nocturnal, orofacial, discoloration, and radicular pains, were present in 110, 60, 96, 99, 36, 56, 43 subjects, respectively vs 53, 13, 35, 27, 12, 11, and 17 of 100 participants in the study by Agrawal et al[12] which also used KPPS as a measure for pain in PD subjects. 11 subjects in our study showed all seven types of pain.

The large prospective PRIAMO study[74] (Parkinson's and nonmotor symptoms) collecting 707 patients and assessing symptoms related to 12 different non-motor domains over 24 months reported that overall non-motor symptoms increase in number along with disease motor severity and duration. Some domains became more prevalent while some domains like psychiatric, cardiovascular, and respiratory symptoms became less prevalent. The frequency and clinical importance of pain however remained stable. Even though our study did not show correlation with disease duration, there was significant association of pain with motor severity.

Patients were taking Levodopa containing regimens in different combinations with Trihexyphenidyl (THP), Pramipexol (PPX), Amantadine (AMTD), Ropinirole (RPNR), Rasagiline (RSGL), Entacapone (ECP), Safinamide and others. One patient was on treatment with only Trihexyphenidyl. Mean LEDD was 920.9 mg ± 563.5 mg

with a maximum equivalent dose of 3214 mg. In the Indian study by Agrawal et al[12], mean LEDD was 414.1 ± 318.9 mg with a maximum equivalent dose of 1577.5 mg. Our study showed weak positive association between KPPS score and LEDD which was statistically significant (r= 0.214, p=0.008). Mean UPDRS score (domain 3) in our study was 20.7 ± 12 vs 15.01 ± 7.55 in their study. These indicate that a higher proportion of patients were on treatment and were at a higher severity of disease in our study. Mean MDS-UPDRS scores were 51.9 ± 25.1 in our study.

In a study by Valkovic et al[67], the presence of pain and severity of depression was compared. Those experiencing any type of pain showed significantly a higher score of BDI (16.6± 9.4 vs. 9.7 ±7.6; p value <0.001), and PDQ-8 (10.1 ± 5.3 vs. 7.0 ± 6.4; p value = 0.02). According to Gao et al[75], the prevalence of sleep disorders in PD patients with pain was 76.1%. Our study also showed a positive correlation between pain and depression as these subjects had a significantly higher score of BDI (11.6±8.1 vs 3.83 ± 6.15; p value <0.004)

In the study by Agrawal et al[12], on correlating KPPS with UPDRS scores by linear regression the UPDRS had positive correlations with an r-value of 0.494 which shows that KPPS scores increase with increase in UPDRS. Our study also had a positive correlation between KPPS and MDS-UPDRS with r-value of 0.47 indicating that pain correlates with increasing motor severity.

Cognition was assessed using MMSE in previous studies by Fu et al[17], Behari et al[11] in PD patients. Our study used MoCA for cognitive assessment which showed a weak association with KPPS (r=-0.19, p=0.015).

In a prospective study by Trenkwalder et al. who showed that intradermal patches of dopamine agonist markedly improved pain[76]. This highlights the fact that proper and early treatment of PD may also improve rigidity and increase the range of movements which could probably decrease the incidence of pain. The difference among mean KPPS of different age groups, gender groups, different LEDD, groups with different disease durations, different drug regimens and were statistically insignificant ($P > 0.05$). Hence pain scores were not affected by the variables such as age, gender, disease duration, LEDD and use of anti-Parkinsonian drugs.

According to Courbon et al[57], the administration of Levodopa markedly raised pain threshold in PD patients but not in healthy subjects. Other studies also revealed that dopamine deficit lowers multimodal pain thresholds that are amenable to correction with Levodopa treatment and dosing. According to Schaeffer et at[77], radicular, neuropathic, or akathisia-related pain may be less responsive to Levodopa, than generalized, nonspecific pain. Clinically, Levodopa alleviated pain in some patients, but exacerbated pain in other patients[78]. LEDD showed weak positive association with KPPS in our study. High LEDD in those with high KPPS scores indicates that Dopaminergic medication alone could not alleviate pain in PD even by dose optimisation.

This prompts further studies that evaluate pain using validated scales in patients receiving dopaminergic therapy.

STRENGTHS:

This is the first south Indian study to establish relation between pain using the internationally validated KPPS and other motor and non-motor components including

depression and cognitive impairment using MDS-UPDRS, NMSS, MOCA and BDI scales. This was the first study to use the Malayalam version of KPPS. Reliability of the Malayalam version was confirmed by retesting after 2 weeks in 50 patients. Another strength of our study was the use of age and sex matched healthy volunteers and comparison with PD patients as most of the previous studies studied the prevalence and characteristics of pain in PD patients in general.

LIMITATIONS:

This study was carried out with a small sample size at a tertiary level movement disorder clinic. Because of the small sample size matching of comorbidities of the patients was not possible. Also, this sample size might not be truly representative of the community distribution. Another limitation is that, there still exists a lack of an objective method of measuring pain perception in patients, as pain is a subjective sensation.

7. CONCLUSIONS

We translated KPPS to Malayalam and established its validity. Our study also established the prevalence of pain which is under detected in PD, and its characteristics. Pain is more in those with more severe motor impairment and more non-motor burden and depression. Our results should encourage treating physicians to assess for pain in PD patients and treat them accordingly.

REFERENCES

8. REFERENCES

1. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006;5:235–245
2. Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. N Engl J Med 1988;318:876 80 .
3. Kalaitzakis ME, Pearce RK. The morbid anatomy of dementia in Parkinson's disease. Acta Neuropathol 2009;118:587-98
4. NH. Lectures on the diseases of the nervous system. Jean Martin Charcot. Lectures on the localisation of cerebral and spinal diseases. Jean Martin Charcot. Neurosurgery 1995;37:1022–1025. .
5. Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci 2002;14:223–236; discussion 222 .
6. Lees AJ, Hardy J and Revesz T (2009) Parkinson's disease. The Lancet 373(9680): 2055–2066
7. Broen MPG, Braaksma MM, Patijn J, et al. (2012) Prevalence of pain in parkinson's disease: A systematic review using the modified Quadas Tool. Movement Disorders 27(4): 480–484.
8. Giovanni D, Alfredo B, Giovanni F, Davide M, et al. Pain as Nonmotor symptom of Parkinson disease. Arch Neurol 2008; 65:191-4
9. Paul BS, Singh A, Jain D, et al. (2016) Assessment of fatigue in parkinson′s disease: Indian perspective. Annals of Indian Academy of Neurology 19(4): 451.
10. Ray Chaudhuri K, Rizos A, Trenkwalder C, et al. King's Parkinson's Disease Pain Scale, The First Scale for Pain in PD. Movement Disorders (2015); 30(12): 1623-31
11. Behari M, Srivastava A, Achtani R, Nandal N, Dutta RB. Pain Assessment in Indian Parkinson's Disease Patients Using King's Parkinson's Disease Pain Scale. Ann Indian Acad Neurol. 2020 Nov-Dec;23(6):774-780. doi: 10.4103/aian.AIAN_449_20 (n.d.).

12. Dhamija RK, Agrawal AK, Anand KS, et al. (2021) Predictors of pain severity and its impact on quality of life in patients with parkinson's disease. Neurology India 69(4): 979
13. Ha AD and Jankovic J (2011) Pain in parkinson's disease. Movement Disorders 27(4): 485–491.
14. Antonini A, Tinazzi M, Abbruzzese G, et al. (2018) Pain in parkinson's disease: Facts and uncertainties. European Journal of Neurology 25(7).
15. M.A. Silverdale, C. Kobylecki, L. Kass-Iliyya, P. Martinez-Martin, M. Lawton, S. Cotterill, K.R. Chaudhuri, H. Morris, F. Baig, N. Williams, L. Hubbard, M.T. Hu, D.G. Grosset, U.K.P.s.P.S. Collaboration, A detailed clinical study of pain in 1957 participants with early/moderate Parkinson's disease, Parkinsonism Relat. Disord. DOI https://doi.org/10.1016/j.parkreldis.2018.06.001(2018)
16. Choi S-M, Kim BC, Jung H-J, et al. (2017) Impact of pain and pain subtypes on the quality of life of patients with parkinson's disease. Journal of Clinical Neuroscience 45: 105–109.
17. Y.T. Fu, C.J. Mao, L.J. Ma, H.J. Zhang, Y. Wang, J. Li, J.Y. Huang, J.Y. Liu, C.F. Liu, Pain correlates with sleep disturbances in Parkinson's disease patients, Pain Pract. 18 (2018) 29–37.
18. G. Defazio, A. Antonini, M. Tinazzi, A.F. Gigante, S. Pietracupa, R. Pellicciari, M. Bloise, R. Bacchin, A. Marcante, G. Fabbrini, A. Berardelli, Relationship between pain and motor and non-motor symptoms in Parkinson's disease, Eur. J. Neurol. 24 (2017) 974–980
19. Braak H, Sastre M, Bohl JRE, et al. Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre- and postganglionic neurons. Acta Neuropathol 2007; 113:421–9.
20. Hagelberg N, Ja¨a¨skela¨inen SK, Martikainen IK, Mansikka H, Forssell H, Scheinin H, Hietala J, Pertovaara A (2004) Striatal dopamine D2 receptors in modulation of pain in humans: a review. Eur J Pharmacol 500(1–3):187–192
21. Rascol O, Zesiewicz T, Chaudhuri KR, Asgharnejad M, Surmann E, Dohin E, et al. A randomized controlled exploratory pilot study to evaluate the efect of rotigotine transdermal patch on Parkinson's disease-associated chronic pain. J Clin Pharmacol. 2016;56:852–61. https://doi.org/10.1002/jcph.678

22. T. Thompson, K. Gallop, C.U. Correll, A.F. Carvalho, N. Veronese, E.Wright, B. Stubbs, Pain perception in Parkinson's disease: a systematic review andmeta-analysis of experimental studies, Ageing Res. Rev. 35 (2017) 74–86. (n.d.).
23. Wasner, G. & Deuschl, G. Pains in Parkinson disease—many syndromes under one umbrella. Nat. Rev. Neurol. 8, 284–294 (2012)
24. Ford B. Pain in Parkinson's disease. Mov Disord 2010; 25 Suppl 1:S98–103. doi: 10.1002/mds.22716 PMID: 20187254
25. Widar M, Samuelsson L, Karlsson-Tivenius S, Ahlstrøm G. Long-term pain conditions after a stroke. J Rehabil Med 2002;34:165–70 .
26. Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosisprevalence and clinical characteristics. Eur J Pain 2005;9:531–42
27. S.R. Snider, S. Fahn, W.P. Isgreen, L.J. Cote, Primary sensory symptoms in parkinsonism, Neurology 26 (1976) 423–429 .
28. C.G. Goetz, C.M. Tanner, M. Levy, R.S. Wilson, D.C. Garron, Pain in Parkinson's disease, Mov. Disord. 1 (1986) 45–49. .
29. M. Tinazzi, C. Del Vesco, E. Fincati, S. Ottaviani, N. Smania, G. Moretto, A. Fiaschi, D. Martino, G. Defazio, Pain and motor complications in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 77 (2006) 822–825. .
30. C.H. Lin, K.R. Chaudhuri, J.Y. Fan, C.I. Ko, A. Rizos, C.W. Chang, H.I. Lin, Y.R. Wu, Depression and Catechol-O-methyltransferase (COMT) genetic variants are associated with pain in Parkinson's disease, Sci. Rep. 7 (2017) 6306
31. M.L. Rabin, M.C. Earnhardt, A. Patel, I. Ganihong, R. Kurlan, Postural, bone, and joint disorders in Parkinson's disease, Mov. Disord. Clin. Pract. 3 (2016) 538–547 .
32. M.A.S. Zella, C. May, T. Muller, M. Ahrens, L. Tonges, R. Gold, K. Marcus, D. Woitalla, Landscape of pain in Parkinson's disease: impact of gender differences, Neurol. Res. DOI 10.1080/01616412.2018.1531208(2018) 1-11
33. R. Papalia, G. Torre, G. Papalia, M.H. Baums, P. Narbona, V. Di Lazzaro, V. Denaro, Frozen shoulder or shoulder stiffness from Parkinson disease?, Musculoskelet. Surg. DOI https://doi.org/10.1007/s12306-018-0567-3(2018) .
34. I. Galazky, C. Caspari, H.J. Heinze, J. Franke, The prevalence of chronic low back pain and lumbar deformities in patients with Parkinson's disease:

implications on spinal surgery, Eur. Spine J. DOI https://doi.org/10.1007/s00586-018-5748-0(2018) .

35. Y.E. Kim, H.J. Kim, J.Y. Yun, W.W. Lee, H.J. Yang, J.M. Kim, B. Jeon, Musculoskeletal problems affect the quality of life of patients with Parkinson's disease, J, Mov. Disord. 11 (2018) 133–138. .
36. M. Kodama, T. Kasahara, M. Hyodo, K. Aono, M. Sugaya, Y. Koyama, K. Hanayama, Y. Masakado, Effect of low-frequency repetitive transcranial magnetic stimulation combined with physical therapy on L-dopa-induced painful off-period dystonia in Parkinson's disease, Am. J. Phys. Med. Rehabil. 90 (2011) 150–155. .
37. I. Rieu, B. Degos, G. Castelnovo, C. Vial, E. Durand, B. Pereira, M. Simonetta-Moreau, S. Sangla, F. Fluchere, D. Guehl, P. Burbaud, C. Geny, D. Gayraud, F. Ory-Magne, F. Bouhour, E. Llinares, P. Derost, A. Marques, F. Durif, Incobotulinum toxin A in Parkinson's disease with foot dystonia: a double blind randomized trial, Parkinsonism Relat. Disord. 46 (2018) 9–15 .
38. J.S. Park, D. Park, P.W. Ko, K. Kang, H.W. Lee, Serum methylmalonic acid correlates with neuropathic pain in idiopathic Parkinson's disease, Neurol. Sci. 38 (2017) 1799–1804. .
39. J.K. Adewusi, M. Hadjivassiliou, A. Vinagre-Aragon, K.R. O'Connor, A. Khan, R.A. Grunewald, P. Zis, Peripheral neuropathic pain in idiopathic Parkinson's disease: prevalence and impact on quality of life; a case controlled study, J. Neurol. Sci. 392 (2018) 3–7. .
40. Z. Chovancova, P. Kanovsky, J. Dufek, M. Nevrly, P. Otruba, Peripheral nerve involvement and severity of motor disorder in Parkinson's disease: a correlational study, Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub. 153 (2009) 59–62.
41. H. Kaur, K. Bhatia, A. Yelam, A. Shukla, I. Asher, R. Govindarajan, Infusion-ratedependent acute neuropathic pain with Duopa in a patient with Parkinson's disease and pre-existing neuropathy, Cureus 10 (2018), e3055 .
42. M. Onofrj, L. Bonanni, G. Cossu, D. Manca, F. Stocchi, A. Thomas, Emergencies in parkinsonism: akinetic crisis, life-threatening dyskinesias, and polyneuropathy

during LDopa gel treatment, Parkinsonism Relat. Disord. 15 (Suppl. 3) (2009) S233–S236. .

43. A. Uncini, R. Eleopra, M. Onofrj, Polyneuropathy associated with duodenal infusion of levodopa in Parkinson's disease: features, pathogenesis and management, J. Neurol. Neurosurg. Psychiatry 86 (2015) 490–495. .
44. G.G. Demerjian, A.B. Sims, B.C. Stack, Proteomic signature of temporomandibular joint disorders (TMD): toward diagnostically predictive biomarkers, Bioinformation 5 (2011) 282–284.
45. Taghizadeh G, Joghataei MT, Goudarzi S, Bakhsheshi M, Habibi SAH, Mehdizadeh M. King's Parkinson's disease pain scale cut-off points for detection of pain severity levels: A reliability and validity study. Neurosci Lett. 2021 Feb 6;745:135620. doi: 10.1016/j.neulet.2020.135620.
46. A.Q. Rana, A.R.M. Qureshi, A. Haris, M.A. Danish, M.S. Furqan, O. Shaikh, Z. Sarfraz, R. Rana, Negative impact of severity of pain onmood, social life and general activity in Parkinson's disease, Neurol. Res. 40 (2018) 1054–1059.
47. A.Q. Rana, A.R.M. Qureshi, Y. Shamli Oghli, Y. Saqib, B. Mohammed, Z. Sarfraz, R. Rana, Decreased sleep quality in Parkinson's patients is associated with higher anxiety and depression prevalence and severity, and correlates with pain intensity and quality, Neurol. Res. 40 (2018) 696–701 .
48. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–138. 41Melzack R, Katz J, Jeans ME. The role of compensation in chronic pain: analysis using a new method of scoring the McGill Pain Questionnaire. Pain 1985;23:101–112.
49. Medical Outcomes Trust. How to score the SF-36 health survey, Boston, 1994.
50. Ghorban Taghizadeh, Mohammad Taghi Joghataei, Sepideh Goudarzi, Merat Bakhsheshi, Sayed Amir Hasan Habibi, Maryam Mehdizadeh, King's Parkinson's disease pain scale cut-off points for detection of pain severity levels: A reliability and validity study, Neuroscience Letters, Volume 745, 2021, 135620, ISSN 0304-3940
51. Jensen, M. P. & Karoly, P. Self-report scales and procedures for assessing pain in adults. In Handbook of pain assessment Self-report scales and procedures for

assessing pain in adults. (eds. Turk, D. C. & Melzack, R.) 15–34 (Guilford Press, 2001)

52. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain 2001;92:147–157
53. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277–299
54. Perez-Lloret S, Ciampi de Andrade D, Lyons KE, Rodríguez-Blázquez C, Chaudhuri KR, Deuschl G, Cruccu G, Sampaio C, Goetz CG, Schrag A, Martinez-Martin P, Stebbins G; Members of the MDS Committee on Rating Scales Development. Rating Scales for Pain in Parkinson's Disease: Critique and Recommendations. Mov Disord Clin Pract. 2016 Jun 24;3(6):527-537. doi: 10.1002/mdc3.12384.
55. Hirsi JO, Yifru YM, Metaferia GZ, Bower JH, Prevalence of pain in patients with Parkinson's disease in Addis Ababa, Ethiopia, Parkinsonism and Related Disorders (2018), doi: https://doi.org/10.1016/j.parkreldis.2018.09.030
56. Martinez-Martin P, Manuel Rojo-Abuin J, Rizos A, Rodriguez-Blazquez C, Trenkwalder C, Perkins L, Sauerbier A, Odin P, Antonini A, Chaudhuri KR; KPPS, EUROPAR and the IPMDS Non Motor PD Study Group. Distribution and impact on quality of life of the pain modalities assessed by the King's Parkinson's disease pain scale. NPJ Parkinsons Dis. 2017 Mar 15;3:8. doi: 10.1038/s41531-017-0009-1.
57. C. Brefel-Courbon, P. Payoux, C. Thalamas, F. Ory, I. Quelven, F. Chollet, J.L. Montastruc, O. Rascol, Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study,Mov. Disord. 20 (2005) 1557–1563. (n.d.).
58. A.R. Qureshi, A.Q. Rana, S.H. Malik, S.F.H. Rizvi, S. Akhter, C. Vannabouathong, Z. Sarfraz, R. Rana, Comprehensive examination of therapies for pain in Parkinson's disease: a systematic review and meta-analysis, Neuroepidemiology 51 (2018) 190–206.
59. Grigoriou S, Martínez-Martín P, Ray Chaudhuri K, Rukavina K, Leta V, Hausbrand D, Falkenburger B, Odin P, Reichmann H. Effects of safinamide on

pain in patients with fluctuating Parkinson's disease. Brain Behav. 2021 Oct;11(10):e2336. doi: 10.1002/brb3.2336.

60. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010 Nov 15; 25:2649–2653. doi: 10.1002/ mds.23429 PMID: 21069833
61. Lin X-J, Yu N, Lin X-G, Zhang Y-F, Chen Y, Zhang K, et al. A clinical survey of pain in Parkinson's disease in Eastern China. Int Psychogeriatr 2016;28:283-9.
62. Rodríguez-Violante M, Alvarado-Bolaños A, Cervantes-Arriaga A, Martinez-Martin P, Rizos A, Chaudhuri KR. Clinical Determinants of Parkinson's Disease-associated Pain Using the King's Parkinson's Disease Pain Scale. Mov Disord Clin Pract. 2017 Feb 6;4(4):545-551. doi: 10.1002/mdc3.12469.
63. Beiske AG, Loge JH, Rønningen A, Svensson E. Pain in Parkinson's disease: Prevalence and characteristics. Pain. 2009 Jan;141(1-2):173-7. doi: 10.1016/j.pain.2008.12.004.
64. Lee MA, Walker RW, Hildreth TJ, Prentice WM. A Survey of Pain in Idiopathic Parkinson's Disease. Journal of Pain and Symptom Management 2006; 32(5): 462-469
65. Tinazzi M, Del Vesco C, Fincati E, et al. Pain and motor complications in Parkinson's disease. J Neurol Neurosurg Psychiatry 2006;77:822–825. doi: 10.1136/jnnp.2005.079053 .
66. Defazio G, Berardelli A, Fabbrini G, et al. Pain as a Nonmotor Symptom of Parkinson Disease. Arch Neurol 2008; 65(9):1191-1194
67. Valkovic, P. et al. Pain in Parkinson's disease: a cross-sectional study of its prevalence, types, and relationship to depression and quality of life. PLoS One 10, e0136541 (2015).
68. Djaldetti R, Shifrin A, Rogowski Z, Sprecher E, Melamed E, Yarnitsky D. Quantitative measurement of pain sensation in patients with Parkinson disease. Neurology 2004;62:2171–2175 .
69. Tinazzi M, Del Vesco C, Defazio G, et al. Abnormal processing of the nociceptive input in Parkinson's disease: a study with CO2 laser evoked potentials. Pain 2008;136:117–124

70. Quinn NP, Koller WC, Lang AE, Marsden CD. Painful Parkinson's disease. Lancet 1986;1:1366–1369
71. Rana AQ, Kabir A, Jesudasan M, Siddiqui I, Khondker S. Pain in Parkinson's disease: analysis and literature review. Clin Neurol Neurosurg. 2013 Nov;115(11):2313-7. doi: 10.1016/j.clineuro.2013.08.022
72. Farnikova K, Krobot A, Kanovsky P. Musculoskeletal problems as an initial manifestation of Parkinson's disease: a retrospective study. J Neurol Sci. 2012 Aug 15;319(1-2):102-4. doi: 10.1016/j.jns.2012.05.002.
73. Defazio, G., Gigante, A., Mancino, P. & Tinazzi, M. The epidemiology of pain in Parkinson's disease. J. Neural Transm. 120, 583–586 (2013)
74. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM, Giglia RM, Iemolo F, Manfredi M, Meco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatrale R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, Dotto PD; PRIAMO study group. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009 Aug 15;24(11):1641-9. doi: 10.1002/mds.22643.
75. Gao L, Huang W, Cai L, Li H. Association between sleep disturbances and pain subtypes in Parkinson's disease. Neurol Sci. 2022 Mar 26. doi: 10.1007/s10072-022-06030-x.
76. Trenkwalder C, Kies B, Rudzinska M, Fine J, et al. Rotigotine effects on early morning motor function and sleep in Parkinson's disease: A double-blind, randomized, placebo-controlled study (RECOVER). Mov Disorder 2001; 26: 90-9
77. Schaeffer E, Berg D. Dopaminergic Therapies for Non-motor Symptoms in Parkinson's Disease. CNS Drugs. 2017 Jul;31(7):551-570. doi: 10.1007/s40263-017-0450-z.
78. Tai YC, Lin CH. An overview of pain in Parkinson's disease. Clin Park Relat Disord. 2019 Nov 28;2:1-8. doi: 10.1016/j.prdoa.2019.11.004.

ANNEXURES

9. ANNEXURES

a. PROFORMA

Study Title: Characterization of pain as a non-motor symptom in Parkinson's disease- a cross sectional observational study from a tertiary care centre in South India

Serial No:

Identification No:

Date of Examination:

Status in Study: **Patient / Healthy Volunteer**

Occupation:

Education:

Age: Gender:

For patients:

Symptoms and Treatment History

Age at Onset Calendar year of Onset:

Side of Onset: Left / Right / Not Sure /

Bilateral Motor Symptoms

1. Tremor
2. Slowness
3. Stiffness
4. Dystonia
5. Gait Disturbance
6. Any other:

Duration of disease at the time of recruitment

Treatment:

No.	Medication	Start date / year	End date / year	Maximum dose tried	Current dose	Comments

Motor fluctuations: Yes / No Duration:

Type of fluctuations

Levodopa Induced Dyskinesia: Yes/ No Duration

Type of Dyskinesia

Early Morning dystonia: Present / Absent

Major Non-motor symptoms

Sleep disturbances Type:

Constipation

Anosmia

Depression

Psychosis

Cognitive symptoms:

Erectile Dysfunction / Urinary Symptoms:

Other Non-motor Symptoms:

A. Examination and Rating Scales

Weight Height Blood Pressure:
Standing Supine

MDS UPDRS Scores (For patients only):

Hoehn and Yahr Stage (For patients only):

MoCA:

Beck's Depression Inventory

NMSS:

Total Score:

Domains Affected

KPPS Scores:

Domain 1:

Domain 2:

Domain 3:

Domain 4:

Domain 5:

Domain 6:

Domain7:

KING'S PD PAIN SCALE

Patient ID No: _____ Initials: _____ DOB: _____

This scale is designed to define and accurately describe the different types and the pattern of pain that your patient may have experienced **during the last month** due to his/her Parkinson's disease or related medication.

Each symptom should be scored with respect to

Severity: 0 = None,
1 = Mild (symptoms present but causes little distress or disturbance to patient),
2 = moderate (some distress or disturbance to patient),
3 = Severe (major source of distress or disturbance to patient).

Frequency: 0 = Never,
1 = Rarely (<1/wk),
2 = Often (1/wk),
3 = Frequent (several times per week),
4 = Very Frequent (daily or all the time).

	Severity (0 – 3)	**Frequency** (0 – 4)	**Frequency x Severity**
Domain 1: Musculoskeletal Pain			
1. Does the patient experience pain around his/her joints? (including arthritic pain)	☐	☐	☐
Domain 1 TOTAL SCORE:			☐
Domain 2: Chronic Pain			
2. Does the patient experience pain deep within the body? (A generalised constant, dull, aching pain – *central pain*)	☐	☐	☐
3. Does the patient experience pain related to an internal organ? (For example, pain around the liver, stomach or bowels – visceral pain)	☐	☐	☐
Domain 2 TOTAL SCORE:			☐
Domain 3: Fluctuation-related Pain			
4. Does the patient experience dyskinetic pain? (pain related to abnormal involuntary movements)	☐	☐	☐
5. Does the patient experience "off" period dystonia in a specific region? (in the area of dystonia)	☐	☐	☐
6. Does the patient experience generalised "off" period pain? (pain in whole body or areas distant to dystonia)	☐	☐	☐
Domain 3 TOTAL SCORE:			☐

KING'S PD PAIN SCALE

	Severity (0 – 3)	Frequency (0 – 4)	Frequency x Severity
Domain 4: Nocturnal Pain			
7. Does the patient experience pain related to jerking leg movements during the night (PLM) or an unpleasant burning sensation in the legs which improves with movement (RLS)?	☐	☐	☐
8. Does the patient experience pain related to difficulty turning in bed at night?	☐	☐	☐
		Domain 4 TOTAL SCORE:	☐
Domain 5: Oro-facial Pain			
9. Does the patient experience pain when chewing?	☐	☐	☐
10. Does the patient have pain due to grinding his/her teeth during the night?	☐	☐	☐
11. Does the patient have burning mouth syndrome?	☐	☐	☐
		Domain 5 TOTAL SCORE:	☐
Domain 6: Discolouration; Oedema/swelling			
12. Does the patient experience a burning pain in his/her limbs? (often associated with swelling or dopaminergic treatment)	☐	☐	☐
13. Does the patient experience generalised lower abdominal pain?	☐	☐	☐
		Domain 6 TOTAL SCORE:	☐
Domain 7: Radicular Pain			
14. Does the patient experience a shooting pain/ pins and needles down the limbs?	☐	☐	☐
		Domain 7 TOTAL SCORE:	☐
		TOTAL SCORE (all domains):	☐

Comments:

പാർക്കിൻസൺസ് രോഗ 'വേദന' സൂചിക

(Kign's PD Pain Scale)

പേര്..... വയസ്സ്.....ID.....

പാർക്കിൻസൺസ് രോഗം നിമിത്തം, കഴിഞ്ഞ ഒരു മാസക്കാലമായി താങ്കൾക്ക് അനുഭവപ്പെട്ട പല വിധത്തിലും തീവ്രതയിലുള്ള 'വേദന' എന്ന ലക്ഷണത്തെക്കുറിച്ച് വിശദമായി രോഖപ്പെടുത്തുന്ന സൂചികയാണിത്.

ഓരോ ചോദ്യങ്ങൾക്കും, ലക്ഷണങ്ങളുടെ കാഠിന്യവും തീവ്രതയും പ്രത്യേകം തന്നെ രേഖപ്പെടുത്തേണ്ടതാണ്.

ലക്ഷണങ്ങളുടെ കാഠിന്യം

0 - ലക്ഷണം ഇല്ല	1- നേരിയ തോതിൽ	2- സാമാന്യം പ്രയാസം	3- കഠിനമായി

ലക്ഷണങ്ങളുടെ ആവർത്തനം

0- ബാധകമല്ല	1- അപൂർവ്വമായി	2- ഇടയ്ക്കിടെ	3- മിക്കവാറും	4- എല്ലായ്പ്പോഴും

വിഭാഗം (എ)

പേശികളും അസ്ഥികളും സംബന്ധിച്ചത്

1) 'സന്ധികൾക്ക് ചുറ്റും വേദന അനുഭവപ്പെടുന്നുണ്ടോ?

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം എ

കാഠിന്യം X ആവർത്തനം		**ആകെ**

വിഭാഗം ബി

ദീർഘനാളായിട്ടുള്ള 'വേദന'യുമായി ബന്ധപ്പെട്ടത്

2. ശരീരത്തിന് ഉള്ളിൽ 'ആഴത്തിൽ'ഉണ്ടാകുന്ന 'വേദന' (പൊതുവേ കാണപ്പെടുന്ന /കോച്ചിപ്പിടിക്കുന്ന വേദന)

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം ബി

കാഠിന്യം X ആവർത്തനം		**ആകെ**

3. ആന്തരികാവയവുമായി ബന്ധപ്പെട്ട ‘വേദന’ അനുഭവപ്പെടുന്നുണ്ടോ?

(കരൾ/ആമാശയം/ശേധനയുമായി ബന്ധമുള്ളത്)

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം ബി

കാഠിന്യം X ആവർത്തനം		**ആകെ**

വിഭാഗം സി

പാർക്കിൻസമ്സ് രോഗ ഔഷധങ്ങളുടെ ഗുണ സമയവുമായി ബന്ധപ്പെട്ട വേദനകൾ

4. മരുന്നിന്റെ പാർശ്വഫലമായ പുളച്ചിൽ അഥവാ നിയന്ത്രിക്കുനാനാകാത്ത ശരീരചലനങ്ങൽ മൂലമുള്ള ‘വേദനകൾ’

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം സി

കാഠിന്യം X ആവർത്തനം		**ആകെ**

5. മരുന്നിന്റെ ഗുണ സമയം നഷ്ടപ്പെടുന്ന സമയത്ത് (ഓഫ് സമയം) ശരീരത്തിൽ ഉണ്ടാകുനന കോച്ചിപിടുത്തം മൂലം ഉണ്ടാകുന്ന ‘വേദന’

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം സി

കാഠിന്യം X ആവർത്തനം		**ആകെ**

6. മരുന്നിന്റെ ഗുണം നഷ്ടപ്പെടുന്ന സമയത്ത് (ഓഫ്) പൊതുവായ ശരീരവേദനകൾ അനുഭവപ്പെടാറുണ്ടോ? (ശരീരമാസകലം വേദന/കോച്ചിപ്പിടുത്തം ബാധകമല്ല)

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം സി

കാഠിന്യം X ആവർത്തനം	**ആകെ**

വിഭാഗം ഡി

ഉറക്കവുമായി ബന്ധപ്പെട്ടവ

7. രാത്രി നേരത്ത് കാലിൽ 'നടുക്കം' അഥവാ 'ഞെട്ടൽ' മുലം ഉണ്ടാകുന്ന വേദന അഥവാ കാലുകൾ ചലിപ്പിക്കുമ്പോൾ കുറയുന്നതും കാൽ ചലിപ്പിക്കാതെ വയ്ക്കുമ്പോൾ കാലിൽ ഉമ്ടാകുന്ന അസ്വസ്ഥത അഥവാ വേദന

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം ഡി

കാഠിന്യം X ആവർത്തനം	**ആകെ**

8. രാത്രിയിൽ തിരിഞ്ഞ് കിടക്കുവാൻ ശ്രമിക്കുമ്പോൾ അനുഭവപ്പെടുന്ന വേദന

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം ഡി

കാഠിന്യം X ആവർത്തനം	**ആകെ**

വിഭാഗം ഇ

മുഖത്തെ പേശികൾക്ക് ഉണ്ടാകുന്ന വേദന

9. പല്ലുകൾ ഉപയോഗിച്ച് ചവയ്ക്കുമ്പോൾ വേദനയുണ്ടോ?

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം ഇ

കാഠിന്യം X ആവർത്തനം		**ആകെ**

10. രാത്രിയിൽ കാണപ്പെടുന്ന 'പല്ലിറുമ്മൽ' മൂലം വേദന ുണ്ടാകുന്നുണ്ടോ?

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം ഇ

കാഠിന്യം X ആവർത്തനം		**ആകെ**

11. വായുടെ ഉള്ളിൽ പുകച്ചിൽ/എരിച്ചിൽ പോലുള്ള പ്രയാസങ്ങൾ ഉണ്ടോ?

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം ഇ

കാഠിന്യം X ആവർത്തനം		**ആകെ**

വിഭാഗം എഫ്

നിറവ്യത്യാസം/നീർക്കെട്ട് അഥവാ നിര് വീക്കം

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം എഫ്

കാഠിന്യം X ആവർത്തനം		**ആകെ**

12. കാലുകളിൽ പുകച്ചിൽ പോലെ അഥവാ മരുന്നുകളുടെ പാർശ്വഫലം മൂലമുണ്ടാകുന്ന നീർവീക്കം മുലമുള്ള പ്രയാസം/വേദന

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം എഫ്

കാഠിന്യം X ആവർത്തനം		**ആകെ**

13. അടിവയറ്റഇൽ തോന്നിക്കുനന പൊതുവേയുള്ല വേദന

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം എഫ്

കാഠിന്യം X ആവർത്തനം		**ആകെ**

വിഭാഗം ജി

കുത്തിയുള്ള അഥവാ തുളയ്ക്കുന്ന വേദന

14. സൂചി മൂലം ഉണ്ടാകുന്നതുപോലെ ഉള്ള തുളയ്ക്കുന്ന വേദന

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

വിഭാഗം ജി

കാഠിന്യം X ആവർത്തനം	**ആകെ**

ആകെ സ്കോർ

കാഠിന്യം	0	1	2	3

ലക്ഷണങ്ങളുടെ ആവർത്തനം	0	1	2	3	4

കാഠിന്യം X ആവർത്തനം	**ആകെ**

International Parkinson and
Movement Disorder Society

MDS-UPDRS

The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale

Authored by:

Christopher G. Goetz
Stanley Fahn
Pablo Martinez-Martin
Werner Poewe
Cristina Sampaio
Glenn T. Stebbins
Matthew B. Stern
Barbara C. Tilley
Richard Dodel
Bruno Dubois
Robert Holloway
Joseph Jankovic
Jaime Kulisevsky
Anthony E. Lang
Andrew Lees
Sue Leurgans
Peter A. LeWitt
David Nyenhuis
Warren Olanow
Olivier Rascol
Anette Schrag
Jeanne A. Teresi
Jacobus J. van Hilten
Nancy LaPelle

Tel +1 (414) 276-2145
Fax +1 (414) 276-3349

555 E. Wells Street, Suite 1100
Milwaukee, WI 53202-3823

www.movementdisorders.org
info@movementdisorders.org

MDS Permissions

The MDS-sponsored revision of the UPDRS (MDS-UPDRS) is owned and licensed by the International Parkinson and Movement Disorder Society (MDS). Permission is required to use the scale and can be obtained by submitting a Permissions Request Form on the MDS website. For licensing inquiries, please e-mail info@movementdisorders.org.

Unauthorized reproduction, distribution, translation, or sale of any portion of the MDS-UPDRS is strictly prohibited. Changes, modifications and derivative works of the scale are not permitted without the express authorization of MDS. Including but not limited to the following, the MDS-UPDRS may not be incorporated into clinical trials, training materials, certification programs, software programs, electronic platforms, electronic medical records, databases, or devices except by permission of MDS.

MDS-UPDRS

The Movement Disorder Society (MDS)-sponsored new version of the UPDRS is founded on the critique that was formulated by the Task Force for Rating Scales in Parkinson's Disease (*Mov Disord* 2003;18:738-750). Thereafter, the MDS recruited a Chairperson to organize a program to provide the Movement Disorder community with a new version of the UPDRS that would maintain the overall format of the original UPDRS, but address issues identified in the critique as weaknesses and ambiguities. The Chairperson identified subcommittees with chairs and members. Each part was written by the appropriate subcommittee members and then reviewed and ratified by the entire group. These members are listed below.

The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerns a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers, and IB is completed by the patient with or without the aid of the caregiver, but independently of the investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity. Of note, the official versions of Part IA, Part IB and Part II of the MDS-UPDRS do not have separate "ON" or "OFF" ratings. However, for individual programs or protocols the same questions can be used separately for "ON" and "OFF". Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

The authors of this new version are:

Chairperson: Christopher G. Goetz
Part I: Werner Poewe (chair), Bruno Dubois, Anette Schrag
Part II: Matthew B. Stern (chair), Anthony E. Lang, Peter A. LeWitt
Part III: Stanley Fahn (chair), Joseph Jankovic, C. Warren Olanow
Part IV: Pablo Martinez-Martin (chair), Andrew Lees, Olivier Rascol, Bob van Hilten
Development Standards: Glenn T. Stebbins (chair), Robert Holloway, David Nyenhuis
Appendices: Cristina Sampaio (chair), Richard Dodel, Jaime Kulisevsky
Statistical Testing: Barbara Tilley (chair), Sue Leurgans, Jean Teresi
Consultant: Stephanie Shaftman, Nancy LaPelle

Contact:
International Parkinson and Movement Disorder Society
555 East Wells Street, Suite 1100
Milwaukee, WI USA 53202

Telephone: 414-276-2145
Email: info@movementdisorders.org

July 1, 2008

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Overview: This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living. There are 13 questions. Part IA is administered by the rater (six questions) and focuses on complex behaviors. Part IB is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.

Part IA:
In administering Part IA, the examiner should use the following guidelines:

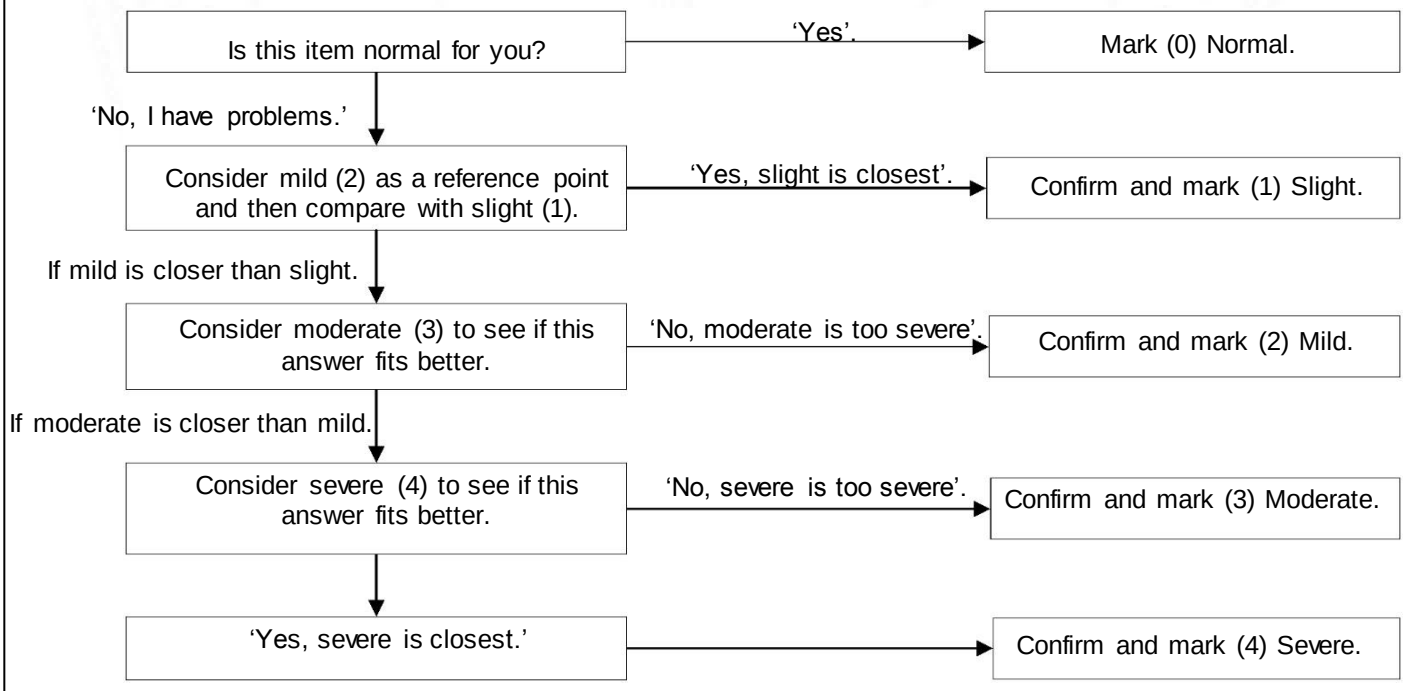
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked **"UR"** for Unable to Rate.
4. The answers should reflect the usual level of function and words such as "usually," "generally," "most of the time" can be used with patients.
5. Each question has a text for you to read (Instructions to patients/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the Instructions to examiner. You should NOT READ the RATING OPTIONS to the patient/caregiver, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.
6. Patients may have co-morbidities and other medical conditions that can affect their function. You and the patient must rate the problem as it exists and do not attempt to separate elements due to Parkinson's disease from other conditions.

EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART IA

Suggested strategies for obtaining the most accurate answer:
After reading the instructions to the patient, you will need to probe the entire domain under discussion to determine normal vs. problematic: If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the patient functions at this level, better or worse. <u>You will not be reading the choices of responses to the patient as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded.</u>

Work up and down the options with the patient to identify the most accurate response, giving a final check by excluding the options above and below the selected response.



Patient Name or Subject ID	Site ID	Assessment Date (mm-dd-yyyy)	Investigator's Initials
_____	_____	_____ - _____ - _____	_____

MDS UPDRS
Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Part IA: Complex behaviors: [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviors that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

1.1 COGNITIVE IMPAIRMENT — **SCORE**

Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver.

Instructions to patient [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town? [If yes, examiner asks patient or caregiver to elaborate and probes for information.]

0: Normal: No cognitive impairment.

1: Slight: Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions. ☐

2: Mild: Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions.

3: Moderate: Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions.

4: Severe: Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.

	SCORE
1.2 HALLUCINATIONS AND PSYCHOSIS Instructions to examiner: Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory, and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patient's insight into hallucinations and identify delusions and psychotic thinking. *Instructions to patient [and caregiver]: Over the past week have you seen, heard, smelled, or felt things that were not really there?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No hallucinations or psychotic behavior. 1: Slight: Illusions or non-formed hallucinations, but patient recognizes them without loss of insight. 2: Mild: Formed hallucinations independent of environmental stimuli. No loss of insight. 3: Moderate: Formed hallucinations with loss of insight. 4: Severe: Patient has delusions or paranoia.	☐
1.3 DEPRESSED MOOD Instructions to examiner: Consider low mood, sadness, hopelessness, feelings of emptiness, or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions. *Instructions to patient [and caregiver]: Over the past week have you felt low, sad, hopeless, or unable to enjoy things? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you carry out your usual activities or to be with people?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No depressed mood. 1: Slight: Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Depressed mood that is sustained over days, but without interference with normal activities and social interactions. 3: Moderate: Depressed mood that interferes with, but does not preclude the patient's ability to carry out normal activities and social interactions. 4: Severe: Depressed mood precludes patient's ability to carry out normal activities and social interactions.	☐

SCORE

1.4 ANXIOUS MOOD

Instructions to examiner: Determine nervous, tense, worried, or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient's ability to carry out daily routines and engage in social interactions.

Instructions to patient [and caregiver]: Over the past week have you felt nervous, worried, or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people? [If yes, examiner asks patient or caregiver to elaborate and probes for information.]

0: Normal: No anxious feelings.

1: Slight: Anxious feelings present but not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions.

2: Mild: Anxious feelings are sustained over more than one day at a time, but without interference with patient's ability to carry out normal activities and social interactions.

3: Moderate: Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions.

4: Severe: Anxious feelings preclude patient's ability to carry out normal activities and social interactions.

1.5 APATHY

Instructions to examiner: Consider level of spontaneous activity, assertiveness, motivation, and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression.

Instructions to patient [and caregiver]: Over the past week, have you felt indifferent to doing activities or being with people? [If yes, examiner asks patient or caregiver to elaborate and probes for information.]

0: Normal: No apathy.

1: Slight: Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions.

2: Mild: Apathy interferes with isolated activities and social interactions.

3: Moderate: Apathy interferes with most activities and social interactions.

4: Severe: Passive and withdrawn, complete loss of initiative.

SCORE

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME

Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g. hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behavior). Rate the impact of such abnormal activities/behaviors on the patient's personal life and on his/her family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity).

Instructions to patient [and caregiver]: Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop? [Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patient.]

0: Normal: No problems present.

1: Slight: Problems are present but usually do not cause any difficulties for the patient or family/caregiver.

2: Mild: Problems are present and usually cause a few difficulties in the patient's personal and family life.

3: Moderate: Problems are present and usually cause a lot of difficulties in the patient's personal and family life.

4: Severe: Problems are present and preclude the patient's ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.

The remaining questions in Part I (Non-motor Experiences of Daily Living) [Sleep, Daytime Sleepiness, Pain and Other Sensation, Urinary Problems, Constipation Problems, Lightheadedness on Standing, and Fatigue] are in the **Patient Questionnaire** along with all questions in Part II [Motor Experiences of Daily Living].

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

SCORE

1.7 SLEEP PROBLEMS

Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning.

0: Normal: No problems.

1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep.

2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep.

3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night.

4: Severe: I usually do not sleep for most of the night.

☐

1.8 DAYTIME SLEEPINESS

Over the past week, have you had trouble staying awake during the daytime?

0: Normal: No daytime sleepiness.

1: Slight: Daytime sleepiness occurs, but I can resist and I stay awake.

2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV.

3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people.

4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.

☐

	SCORE
1.9 PAIN AND OTHER SENSATIONS Over the past week, have you had uncomfortable feelings in your body like pain, aches, tingling, or cramps? 0: Normal: No uncomfortable feelings. 1: Slight: I have these feelings. However, I can do things and be with other people without difficulty. 2: Mild: These feelings cause some problems when I do things or am with other people. 3: Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people. 4: Severe: These feelings stop me from doing things or being with other people.	☐
1.10 URINARY PROBLEMS Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents? 0: Normal: No urine control problems. 1: Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities. 2: Mild: Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents. 3: Moderate: Urine problems cause a lot of difficulties with my daily activities, including urine accidents. 4: Severe: I cannot control my urine and use a protective garment or have a bladder tube.	☐

	SCORE
1.11 CONSTIPATION PROBLEMS Over the past week have you had constipation troubles that cause you difficulty moving your bowels? 0: Normal: No constipation. 1: Slight: I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable. 2: Mild: Constipation causes me to have some troubles doing things or being comfortable. 3: Moderate: Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything. 4: Severe: I usually need physical help from someone else to empty my bowels.	☐
1.12 LIGHT HEADEDNESS ON STANDING Over the past week, have you felt faint, dizzy, or foggy when you stand up after sitting or lying down? 0: Normal: No dizzy or foggy feelings. 1: Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things. 2: Mild: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down. 3: Moderate: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling. 4: Severe: Dizzy or foggy feelings cause me to fall or faint.	☐

	SCORE
1.13 FATIGUE Over the past week, have you usually felt fatigued? This feeling is <u>not</u> part of being sleepy or sad. 0: Normal: No fatigue. 1: Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people. 2: Mild: Fatigue causes me some troubles doing things or being with people. 3: Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything. 4: Severe: Fatigue stops me from doing things or being with people.	☐

Part II: Motor Aspects of Experiences of Daily Living (M-EDL)

2.1 SPEECH Over the past week, have you had problems with your speech? 0: Normal: Not at all (no problems). 1: Slight: My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself. 2: Mild: My speech causes people to ask me to occasionally repeat myself, but not every day. 3: Moderate: My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood. 4: Severe: Most or all of my speech cannot be understood.	☐

	SCORE
2.2 SALIVA AND DROOLING Over the past week, have you usually had too much saliva during when you are awake or when you sleep? 0: Normal: Not at all (no problems). 1: Slight: I have too much saliva, but do not drool. 2: Mild: I have some drooling during sleep, but none when I am awake. 3: Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief. 4: Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.	☐
2.3 CHEWING AND SWALLOWING Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped, or blended to avoid choking? 0: Normal: No problems. 1: Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared. 2: Mild: I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week. 3: Moderate. I choked at least once in the past week. 4: Severe: Because of chewing and swallowing problems, I need a feeding tube.	☐

	SCORE
2.4 EATING TASKS Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knives, spoons, chopsticks? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need any help handling my food and have not had food spills while eating. 2: Mild: I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat. 3: Moderate: I need help with many eating tasks but can manage some alone. 4: Severe: I need help for most or all eating tasks.	☐
2.5 DRESSING Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need help. 2: Mild: I am slow and need help for a few dressing tasks (buttons, bracelets). 3: Moderate: I need help for many dressing tasks. 4: Severe: I need help for most or all dressing tasks.	☐

	SCORE
2.6 HYGIENE Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair, or with other personal hygiene? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need any help. 2: Mild: I need someone else to help me with some hygiene tasks. 3: Moderate: I need help for many hygiene tasks. 4: Severe: I need help for most or all of my hygiene tasks.	☐
2.7 HANDWRITING Over the past week, have people usually had trouble reading your handwriting? 0: Normal: Not at all (no problems). 1: Slight: My writing is slow, clumsy or uneven, but all words are clear. 2: Mild: Some words are unclear and difficult to read. 3: Moderate: Many words are unclear and difficult to read. 4: Severe: Most or all words cannot be read.	☐
2.8 DOING HOBBIES AND OTHER ACTIVITIES Over the past week, have you usually had trouble doing your hobbies or other things that you like to do? 0: Normal: Not at all (no problems). 1: Slight: I am a bit slow but do these activities easily. 2: Mild: I have some difficulty doing these activities. 3: Moderate: I have major problems doing these activities, but still do most. 4: Severe: I am unable to do most or all of these activities.	☐

	SCORE
2.9 TURNING IN BED Over the past week, do you usually have trouble turning over in bed? 0: Normal: Not at all (no problems). 1: Slight: I have a bit of trouble turning, but I do not need any help. 2: Mild I have a lot of trouble turning and need occasional help from someone else. 3: Moderate: To turn over I often need help from someone else. 4: Severe: I am unable to turn over without help from someone else.	☐
2.10 TREMOR Over the past week, have you usually had shaking or tremor? 0: Normal: Not at all. I have no shaking or tremor. 1: Slight: Shaking or tremor occurs but does not cause problems with any activities. 2: Mild: Shaking or tremor causes problems with only a few activities. 3: Moderate: Shaking or tremor causes problems with many of my daily activities. 4: Severe: Shaking or tremor causes problems with most or all activities.	☐
2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair? 0: Normal: Not at all (no problems). 1: Slight: I am slow or awkward, but I usually can do it on my first try. 2: Mild: I need more than one try to get up or need occasional help. 3: Moderate: I sometimes need help to get up, but most times I can still do it on my own. 4: Severe: I need help most or all of the time.	☐

	SCORE
2.12 WALKING AND BALANCE Over the past week, have you usually had problems with balance and walking? 0: Normal: Not at all (no problems). 1: Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2: Mild: I occasionally use a walking aid, but I do not need any help from another person. 3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4: Severe: I usually use the support of another person to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor? 0: Normal: Not at all (no problems). 1: Slight: I briefly freeze, but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing. 3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help. 4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	☐

This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see." Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables), and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction, or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling, and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

SCORE

3.3 RIGIDITY

Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

0: Normal: No rigidity.

1: Slight: Rigidity only detected with activation maneuver.

2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.

3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.

4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.

☐ Neck

☐ RUE

☐ LUE

☐ RLE

☐ LLE

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.

2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.

3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.

☐ R

☐ L

SCORE

3.5 HAND MOVEMENTS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.

R ☐

L ☐

3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down, and then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st supination-pronation sequence.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.

R ☐

L ☐

SCORE

3.7 TOE TAPPING

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.

2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the 1st tap.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

3.8 LEG AGILITY

Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the 1st tap.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.

☐ R

☐ L

	SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt up to a maximum of two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13. 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from the arms of the chair without difficulty. 3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using the arms of the chair, but can get up without help. 4: Severe: Unable to arise without help.	☐
3.10 GAIT Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13. 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	☐

	SCORE
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning, or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning, or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3: Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	☐
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13. 0: Normal: No problems. Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

SCORE

3.16 KINETIC TREMOR OF THE HANDS

Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen.

0: Normal:	No tremor.	
1: Slight:	Tremor is present but less than 1 cm in amplitude.	R
2: Mild:	Tremor is at least 1 but less than 3 cm in amplitude.	
3: Moderate:	Tremor is at least 3 but less than 10 cm in amplitude.	
4: Severe:	Tremor is at least 10 cm in amplitude.	L

3.17 REST TREMOR AMPLITUDE

Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking, and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor.
As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating.

Extremity ratings

0: Normal:	No tremor.	RUE
1: Slight:	< 1 cm in maximal amplitude.	
2: Mild:	≥ 1 cm but < 3 cm in maximal amplitude.	LUE
3: Moderate:	≥ 3 cm but < 10 cm in maximal amplitude.	
4: Severe:	≥ 10 cm in maximal amplitude.	RLE

Lip/Jaw ratings

0: Normal:	No tremor.	LLE
1: Slight:	< 1 cm in maximal amplitude.	
2: Mild:	≥ 1 cm but < 2 cm in maximal amplitude.	
3: Moderate:	≥ 2 cm but < 3 cm in maximal amplitude.	Lip/Jaw
4: Severe:	≥ 3 cm in maximal amplitude.	

3.18 CONSTANCY OF REST TREMOR

SCORE

Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

0: Normal: No tremor.

1: Slight: Tremor at rest is present ≤ 25% of the entire examination period.

2: Mild: Tremor at rest is present 26-50% of the entire examination period.

3: Moderate: Tremor at rest is present 51-75% of the entire examination period.

4: Severe: Tremor at rest is present > 75% of the entire examination period.

☐

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes

B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes

HOEHN AND YAHR STAGE

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.

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

5: Wheelchair bound or bedridden unless aided.

☐

Part IV: Motor Complications

Overview and Instructions: In this section, the rater uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place "**UR"** for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours the patient is generally awake and use this figure as the denominator for "OFF" time and dyskinesias. For "OFF dystonia", the total "OFF" time will be the denominator. Operational definitions for examiner's use.

Dyskinesias: Involuntary random movements:
Words that patients often recognize for dyskinesias include "irregular jerking", "wiggling", "twitching." It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: Contorted posture, often with a twisting component:
Words that patients often recognize for dystonia include "spasms", "cramps", "posture."

Motor fluctuation: Variable response to medication:
Words that patients often recognize for motor fluctuation include "wearing out", "wearing off", "roller-coaster effect", "on-off", "uneven medication effects."

OFF: Typical functional state when patients have a poor response in spite of taking mediation or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include "low time", "bad time", "shaking time", "slow time", "time when my medications don't work."

ON: Typical functional state when patients are receiving medication and have a good response:
Words that patients often recognize include "good time", "walking time", "time when my medications work."

A. DYSKINESIAS [exclusive of OFF-state dystonia]

SCORE

4.1 TIME SPENT WITH DYSKINESIAS

Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

Instructions to patient [and caregiver]: Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ____ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching, or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking, and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ____ (use this number for your calculations).

0:	Normal:	No dyskinesias.
1:	Slight:	≤ 25% of waking day.
2:	Mild:	26 - 50% of waking day.
3:	Moderate:	51 - 75% of waking day.
4:	Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours with Dyskinesia: _____
3. % Dyskinesia = ((2/1)*100): _____

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS

SCORE

Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?

0: Normal:	No dyskinesias or no impact by dyskinesias on activities or social interactions.
1: Slight:	Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
2: Mild:	Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
3: Moderate:	Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes.
4: Severe:	Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.

B. MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6.

Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time, or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are generally awake ____ hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function? ____ (use this number for your calculations).

0: Normal:	No OFF time.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours OFF: _____
3. % OFF = ((2/1)*100): _____

	SCORE
4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer. *Instructions to patient [and caregiver]: Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?* 0: Normal: No fluctuations or no impact by fluctuations on performance of activities or social interactions. 1: Slight: Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state. 2: Mild: Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state. 3: Moderate: Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods. 4: Severe: Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.	☐
4.5 COMPLEXITY OF MOTOR FLUCTUATIONS Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake, or other factors. Use the information provided by the patients and caregivers and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time, or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer. *Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"* 0: Normal: No motor fluctuations. 1: Slight: OFF times are predictable all or almost all of the time (> 75%). 2: Mild: OFF times are predictable most of the time (51-75%). 3: Moderate: OFF times are predictable some of the time (26-50%). 4: Severe: OFF episodes are rarely predictable (≤ 25%).	☐

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have ____ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ____ hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0: Normal: No dystonia OR NO OFF TIME.

1: Slight: ≤ 25% of time in OFF state.

2: Mild: 26-50% of time in OFF state.

3: Moderate: 51-75% of time in OFF state.

4: Severe: > 75% of time in OFF state.

1. Total Hours OFF:	_____
2. Total OFF Hours with Dystonia:	_____
3. % OFF Dystonia = ((2/1)*100):	_____

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

Patient Name or Subject ID	Site ID	Assessment Date (mm-dd-yyyy)	Investigator's Initials
_____	____ ____ ____	____ - ____ - ____	____ ____ ____

MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	
			3.7a	Toe tapping– Right foot	
1.7	Sleep problems		3.7b	Toe tapping– Left foot	
1.8	Daytime sleepiness		3.8a	Leg agility– Right leg	
1.9	Pain and other sensations		3.8b	Leg agility– Left leg	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatigue		3.12	Postural stability	
Part II			3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chewing and swallowing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handwriting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	
2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest tremor	
2.12	Walking and balance			Were dyskinesias present?	☐ No ☐ Yes
2.13	Freezing			Did these movements interfere with ratings?	☐ No ☐ Yes
3a	Is the patient on medication?	☐ No ☐ Yes		Hoehn and Yahr Stage	
3b	Patient's clinical state	☐ Off ☐ On	**Part IV**		
3c	Is the patient on levodopa?	☐ No ☐ Yes	4.1	Time spent with dyskinesias	
3.C1	If yes, minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	

Non-Motor Symptom assessment scale for Parkinson's Disease

Patient ID No: _____ **Initials:** _____ **Age:** _____

Symptoms assessed over the last month. Each symptom scored with respect to:

Severity: 0 = None, 1 = Mild: symptoms present but causes little distress or disturbance to patient; 2 = Moderate: some distress or disturbance to patient; 3 = Severe: major source of distress or disturbance to patient.

Frequency: 1 = Rarely (<1/wk); 2 = Often (1/wk); 3 = Frequent (several times per week); 4 = Very Frequent (daily or all the time)

Domains will be weighed differentially. Yes/ No answers are not included in final frequency x severity calculation.
(Bracketed text in questions within the scale is included as an explanatory aid).

Domain 1: Cardiovascular including falls	**Severity**	**Frequency**	**Frequency x Severity**
1. Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?	☐	☐	☐
2. Does the patient fall because of fainting or blacking out?	☐	☐	☐
SCORE:			☐

Domain 2: Sleep/fatigue			
3. Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reding).	☐	☐	☐
4. Does fatigue (tiredness) or lack of energy (not slowness) limit the patient's daytime activities?	☐	☐	☐
5. Does the patient have difficulties falling or staying asleep?	☐	☐	☐
6. Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?	☐	☐	☐
SCORE:			☐

Domain 3: Mood /Cognition			
7. Has the patient lost interest in his/her surroundings?	☐	☐	☐
8. Has the patient lost interest in doing things or lack motivation to start new activities?	☐	☐	☐
9. Does the patient feel nervous, worried or frightened for no apparent reason?	☐	☐	☐
10. Does the patient seem sad or depressed or has he/she reported such feelings?	☐	☐	☐
11. Does the patient have flat moods without the normal "highs" and " lows"?	☐	☐	☐
12. Does the patient have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure?	☐	☐	☐
SCORE:			☐

Domain 4: Perceptual problems/hallucinations			
13. Does the patient indicate that he/she sees things that are not there?	☐	☐	☐
14. Does the patient have beliefs that you know are not true? (For example, about being harmed, being robbed or being unfaithful)	☐	☐	☐
15. Does the patient experience double vision? (2 separate real objects and not blurred vision)	☐	☐	☐
SCORE:			☐

	Severity	Frequency	Frequency x Severity
Domain 5: Attention/ Memory			
16. Does the patient have problems sustaining concentration during activities? (For example, reading or having a conversation)	☐	☐	☐
17. Does the patient forget things that he/she has been told a short time ago or events that happened in the last few days?	☐	☐	☐
18. Does the patient forget to do things? (For example, take tablets or turn off domestic appliances?)	☐	☐	☐
SCORE:			☐
Domain 6: Gastrointestinal tract			
19. Does the patient dribble saliva during the day?	☐	☐	☐
20. Does the patient having difficulty swallowing?	☐	☐	☐
21. Does the patient suffer from constipation? (Bowel action less than three times weekly)	☐	☐	☐
SCORE:			☐
Domain 7: Urinary			
22. Does the patient have difficulty holding urine? (Urgency)	☐	☐	☐
23. Does the patient have to void within 2 hours of last voiding? (Frequency)	☐	☐	☐
24. Does the patient have to get up regularly at night to pass urine? (Nocturia)	☐	☐	☐
SCORE:			☐
Domain 8: Sexual function			
25. Does the patient have altered interest in sex? (Very much increased or decreased, please underline)	☐	☐	☐
26. Does the patient have problems having sex?	☐	☐	☐
SCORE:			☐
Domain 9: Miscellaneous			
27. Does the patient suffer from pain not explained by other known conditions? (Is it related to intake of drugs and is it relieved by antiparkinson drugs?)	☐	☐	☐
28. Does the patient report a change in ability to taste or smell?	☐	☐	☐
29. Does the patient report a recent change in weight (not related to dieting)?	☐	☐	☐
30. Does the patient experience excessive sweating? (not related to hot weather)	☐	☐	☐
SCORE:			☐
TOTAL SCORE:			☐

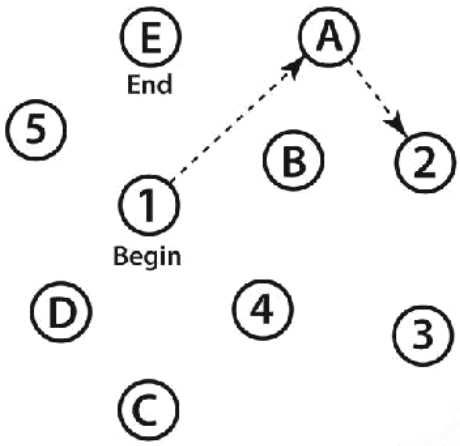
Developed by the International Parkinson's Disease Non- Motor Group.

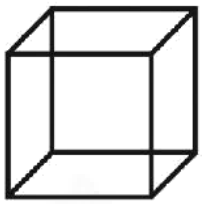
MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE





Copy cube

[ ] [ ]

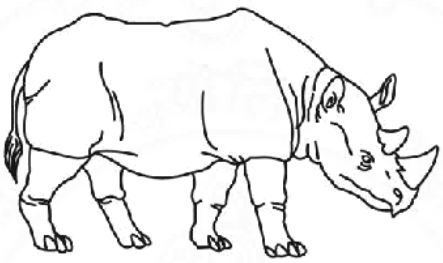
Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

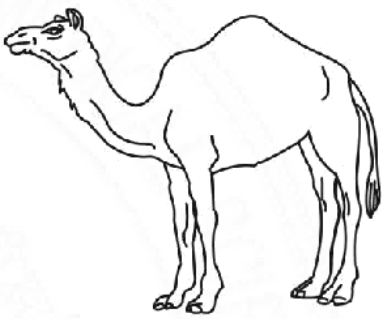
POINTS ___/5

NAMING

[ ]



[ ]



[ ]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]
Optional	Category cue					
	Multiple choice cue					

Points for UNCUED recall only

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
- 0 I do not feel sad.
- 1 I feel sad
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.

0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score	Levels of Depression
1-10	These ups and downs are considered normal
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
over 40	Extreme depression

)

Work Order No. 281081
Under Master User License Agreement

This Work Order is issued under the Master User License Agreement by and between Mapi Research Trust ("MRT") and Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India ("User"). Upon execution by both Parties, together with the **Master User License Agreement dated 27 April 2020** ("MULA"), this Work Order identifies and governs the licensing by MRT of the COA referenced herein ("COA"), and is made a part of and is subject to the MULA.

This Work Order ("WO") is in addition to any and all previous Work Orders under the MULA.

This WO includes the terms and conditions of the MULA, which are hereby incorporated by this reference as though the same was set forth in its entirety and shall be effective as of the WO Effective Date set forth herein.

All capitalized terms which are not defined herein shall have the same meanings as set forth in the MULA.

This WO, including all attachments and the MULA contain the entire understanding of the Parties with respect to the subject matter herein and supersedes all previous agreements and undertakings with respect thereto. If the terms and conditions of this WO or any attachment conflict with the terms and conditions of the MULA, the terms and conditions of the MULA will control, unless this WO specifically acknowledges the conflict and expressly states that the conflicting term or provision found in this WO controls for this WO only. This WO may be modified only by written agreement signed by the Parties.

1. User information

MULA Reference	Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India_IN_280448_MULA-FE
User name	Syam Krishnan Nair
Category of User	University
User address	Sree Chitra Tirunal Institute (SCTIMST), Medical College PO, Thiruvananthapuram, Kerala, 695011 Thiruvananthapuram Kerala, India
User VAT number	
User email	drsyam@sctimst.ac.in
User phone	+919847310745
Billing Information (if different from the above)	Legal form: Address: Country: VAT number (if applicable): Addressee: PO number of internal reference (if applicable):

2. WO information

WO Number	281081
WO Effective Date	Last date of signature of this WO by the Parties
WO Expiration Date ("Term")	X Fixed-term license: upon completion of the Stated Purpose, as defined in 4.1
Name of User's contact in charge of the WO	Dr Syam Krishnan Nair

3. Identification of the COA

Name of the COA	KPPS - King's Parkinson's Disease Pain Scale
Author	Chaudhuri KR,Trenkwalder C,Martinez-Martin P
Copyright Holder	Professor K Ray-Chaudhuri, Professor C Trenkwalder, P Martinez-Martin
Copyright notice	KPPS K Ray-Chaudhuri, C Trenkwalder, P Martinez-Martin, 2012. All Rights Reserved
Bibliographic reference	Chaudhuri KR, Rizos A, Trenkwalder C, Rascol O, Pal S, Martino D, Carroll C, Paviour D, Falup-Pecurariu C, Kessel B, Silverdale M, Todorova A, Sauerbier A, Odin P, Antonini A, Martinez-Martin P; EUROPAR and the IPMDS Non Motor PD Study Group. King's Parkinson's disease pain scale, the first scale for pain in PD: An international validation. Mov Disord. 2015 Oct;30(12):1623-31. (PubMed Abstract: http://www.ncbi.nlm.nih.gov/pubmed/26096067)
Module(s)/version(s) needed	KPPS

4. Context of use of the COA

The User undertakes to use the COA solely in the context of the Stated Purpose as defined hereafter.

4.1 Stated Purpose

Clinical research

Title	Characterization of pain as a non-motor symptom in Parkinson s disease- a cross sectional observational study from a tertiary care center in South India
Study/protocol reference	
Sponsor	No sponsors. It is a non-funded study

Disease or condition	Parkinson's disease
Type of research	Observational
COA used as primary end point	Yes
Number of enrolled patients/subjects	300
Number of estimated failed patients/subjects	
Number of submissions of the COA for each patient	1
Planned Term*	Start: 07/2020; End: 07/2023
Mode of Administration*	paper
If electronic administration, please indicate mode of data collection	
Use of IT Company (e-vendor)	No

4.2 Language versions

4.2.1 Country and languages

MRT grants the License to use the COA on the following countries and in the languages indicated in the table below:

Language	For use in the following country	Availability
Malayalam	India	No

4.2.2 New translation(s) to be produced by the User in language(s) not already available

4.2.2.1 Linguistic validation methodology

Each new translation must undergo a full linguistic validation process according to standard recognized methodology of translation, as described in Acquadro C, Conway K; Giroudet C, Mear I. Linguistic Validation Manual for Health Outcome Assessments. Mapi Institute, 2012.

The recommended methodology includes the following steps:

- Forward translation ;
- Backward translation ;
- Review by clinicians ;
- Cognitive interviews ;
- International harmonization (if more than one language is involved) ;
- Proofreading ;
- Report.

4.2.2.2 Translation process

Academic Purposes

For academic translations, the User shall follow the linguistic validation guidelines and recommendations provided by MRT after the signature of this WO.
Academic translations are considered for academic research and evaluation purposes only. Under no circumstances shall such translations be used for commercial or international studies, or distributed to any third party for commercial or other use.

The User understands and agrees that the copyright on all translations created shall belong to the Copyright Holder.

The User understands and agrees that MRT may provide third parties with the User contact information to allow such third parties to contact the User about questions related to the translation produced by the User.

If the translation work must be abandoned, cancelled or delayed for any reason, the User shall notify MRT immediately.

If MRT does not receive the new translation within 6 (six) months after the anticipated date of completion, the translation will be deemed non-existent and MRT shall be able to authorize other parties to develop the same translations.

MRT shall not be held responsible in case of publication on the same COA by another user. The User shall be responsible for checking the literature before publishing.

4.2.2.3 Provision of the new translation(s) to MRT

Upon completion, the User shall provide MRT with the new translation(s) in one standard exploitable format (i.e. DOC), and one read-only file format (i.e. PDF), therefore allowing MRT to check whether the standard format has undergone any font or character modifications during possible conversions.

The User shall provide a certificate of translation and/or a report with each new translation describing the translation process used for this language.

MRT shall be granted the exclusive right to the distribution of all new translations of the COA. Therefore, the User shall not directly provide any third party with the new translation(s).

The Parties agree that all non-validated translations will be made available by MRT to academics or clinicians only for national use. If such translation is requested by profit making companies for international use, the latter will be obligated to perform a full validation process as per Section 4.2.2.1 of this WO.

In case of publication mentioning use and/or development of such translation, said publication shall not include a copy of the translation in the publication but shall refer to MRT for permission to access and use.

5. Price and payment terms

5.1 License

In consideration for the License granted under this WO, the User agrees to pay the following amount: **not applicable because non-funded academic user**

6. Specific requirements for the COA

● The Copyright Holder of the COA has granted ICON LS exclusive rights to translate the COA in the context of commercial studies or any project funded by for-profit entities. ICON LS is the only organization authorized to perform linguistic validation/translation work on the COA.

● In case the User wants to use an e-Version of the COA, the User shall send the Screenshots of the original version of the COA to MRT or ICON LS for review and approval. The Screenshots review may incur additional fees.

● In case the User wants to use an e-Version of the COA, ICON LS shall update (if needed) and populate the COA translations into the User's or IT Company's system and the User shall send the Screenshots of the translations of the COA to ICON LS for approval. The update (if needed), population of translations and the Screenshots review may incur additional fees.

EXECUTED, as of the WO Effective Date, by the duly authorized representatives as set forth below.

MAPI RESEARCH TRUST

Signature :
Name : Sonia Bothorel
Title :
Date: 28 Apr 2020 11:44:048+0000

Sonia Bothorel

REASON: I approve this document

35c1b998-025e-494e-a2ba-d19efb49f8f2

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, THIRUVANANTHAPURAM, KERALA, INDIA

Signature :

Name : Dr Syam Krishnan Nair
Title : Professor of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India
Phone: +91-9847310745
+91-471-2524268
Email: drsyam@sctimst.ac.in
Date : 28/04/2020

January 4, 2021

Dr. Syam Krishnan Nair
Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST)
Jai Nagar W Rd Chalakkuzhi, Thiruvananthapuram
695011, Kerala
India
T: +91 471 252 4268
E: drsyam@sctimst.ac.in

Re: Authorization to Use Materials Owned by the International Parkinson and Movement Disorder Society (MDS)

Dear Dr. Krishnan Nair:

Thank you for your interest in the MDS Unified Parkinson's Disease Rating Scale ("MDS-UPDRS") and the Non-Motor Symptoms Scale for Parkinson's Disease ("NMSS"). MDS grants permission for use of the MDS-UPDRS and NMSS in English within the study titled, "Characterization of pain as a non-motor symptom in Parkinson's disease- a cross sectional observational study from a tertiary care centre in South India," led by senior resident, Dr. Prabhu As under the academic supervision of you, Dr. Syam Krishnan Nair, at SCTIMST. This study is identified by the ethics committee number: SCT/IEC/1592/DECEMBER-2020. As a residency research study, there is no licensing fee for this use.

By submitting your request to MDS, you agreed to the following:

I understand that the MDS-UPDRS and NMSS may only be used in paper format for the purposes described above. I also understand that reproduction, distribution, translation, or sale of any portion of the MDS-UPDRS and NMSS is strictly prohibited. Changes, modifications, adaptations, and derivative works of the MDS-UPDRS and NMSS are not permitted without the permission of MDS. Furthermore, the MDS-UPDRS and NMSS may not be incorporated into clinical trials, training materials, certification programs, software programs, electronic platforms or otherwise except through express authorization of MDS and payment of any applicable fees. Further, MDS shall have no liability related to use of the MDS-UPDRS and NMSS or any other MDS owned rating scale, and I hereby release, hold harmless, and indemnify MDS, its officers, directors, employees, volunteers, and agents, from any loss, damage, or claim based on such use.

Please do not hesitate to contact me with any questions or concerns.

Sincerely,

Shazia Ali
Director of Scientific Programs
International Parkinson and Movement Disorder Society
ratingscales@movementdisorders.org

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेंद्रम - 695 011, केरल, भारत
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
TRIVANDRUM - 695 011, KERALA, INDIA
(एक राष्ट्रीय महत्व का संस्थान, विज्ञान एवं प्रौद्योगिकी विभाग, भारत सरकार)
(An Institution of National Importance, Department of Science and Technology, Government of India)
टेलीफॉन नं./Telephone No.: 0471-2443152 फैक्स/Fax: 0471-2446433, 2550728
ई-मेल/E-mail: sct@sctimst.ac.in वेबसाइट/Website: www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1592/DECEMBER-2020 19.12.2020

Dr. AS Prabhu
Senior Resident
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. AS Prabhu,

Thank you for submitting documents related to your proposal titled "**CHARACTERIZATION OF PAIN AS A NON-MOTOR SYMPTOM IN PARKINSON'S DISEASE- A CROSS SECTIONAL OBSERVATIONAL STUDY FROM A TERTIARY CARE CENTER IN SOUTH INDIA** (IEC/1592)" to the IEC for review.

The following documents were reviewed:

1. Check list (Not attached)
2. Covering letter addressed to Chairman, IEC, SCTIMST dated 08.08.2020
3. Project Proposal
4. Singed IEC Application
5. Forwarding letter from HoD Dr.Sanjeev Thomas dated 09/08/2020 & Letter from Dr. Syam dated 09/08/2020 addressed to the Chairman, IEC, SCTIMST
6. Proforma
7. Declaration Form
8. Dean's Signature Form
9. TAC Approval Letter with Comments and responses
10. Patient questionnaire
11. Information sheet (English)
12. Information sheet (Malayala
13. Information sheet and informed consent form (English)
14. Information sheet and informed consent form (Malayalam)
15. Invitation for participation in a research study as a healthy volunteer (English)
16. Invitation for participation in a research study as a healthy volunteer (Malayalam)
17. Signed CV of PI Dr.Prabhu with TMC Registration number
18. Signed of Dr.Syam with TCMC Number
19. Signed CV of Dr. Asha Kishore with TCMC Number
20. Signed CV of Dr. Divya KP with TCMC Number
21. Signed CV of Dr. Asha Kishore with TCMC Number
22. Signed CV of Mr.Gangadara Sarma

The following members of the Students Sub-Committee of the Institutional Ethics Committee participated in the discussions held between August 23-October 29, 2020 at the offices and residences of the members

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
5.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision
The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

Plagiarism Checker X - Report

Originality Assessment

Overall Similarity: **3%**

Date: Aug 14, 2022

Statistics: 249 words Plagiarized / 8636 Total words

Remarks: Low similarity detected, check your supervisor if changes are required.