PREVALENCE AND SPECTRUM OF PAIN IN PARKINSON'S DISEASE

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CERTIFICATE

This is to certify that the dissertation title **"PREVALENCE AND SPECTRUM OF PAIN IN PARKINSON'S DISEASE"** is the bonafide original work of **Dr.SREENIVAS.U.M.** in partial fulfilment of the requirements for M.D. Branch - I (General Medicine) Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in APRIL 2017. The Period of study was from April 2016 to September 2016.

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DECLARATION

I, **Dr. SREENIVAS.U.M.** solemnly declare that the dissertation titled **"PREVALENCE AND SPECTRUM OF PAIN IN PARKINSON'S DISEASE"** is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during April 2015 to September 2015 under the guidance and supervision of my unit chief Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to Tamilnadu Dr. M.G.R. Medical University towards partial fulfilment of requirement for the award of **M.D. Degree (Branch - I) in General Medicine - APRIL 2017.**

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CONTENTS

INTRODUCTION

INTRODUCTION

Parkinson's Disease is one of the most debilitating neurological diseases with a profound effect on quality of life. The motor components of Parkinson's disease have been well documented and extensively studied. Most of the treatment of Parkinson's disease has been aimed at the management of motor complications with a view to improving quality of life. However in advanced stages of Parkinson's, the manifestation of non-motor symptoms becomes much more apparent and their management gains prominence.

Pain is one of the recognised non-motor symptoms of Parkinson's Disease. However not much research has been done into definitively defining pain in Parkinson's or its management. Keeping in mind the debilitating potential of pain by itself, it needs more extensive research to define the severity of pain and its presentation in Parkinson's Disease.

Keeping in mind the irreversible nature of Parkinson's disease and the improved treatment of the disease in the community owing to better healthcare coverage, more and more patients are now surviving into the advanced stages of Parkinson's Disease.

Hence the management of non-motor complications is gaining importance.

In this study we attempt to study the prevalence of pain in patients with Parkinson's Disease along with the epidemiology and define the severity and the type of pain. We also look at the relationship of the pain to the Parkinsonian treatment and the response to the same.

AIMS AND OBJECTIVES

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1. To analyse the prevalence of pain in patients with Parkinson's Disease

2. To analyse the type and severity of pain when present in Parkinson's Disease

3. To look into the correlation of pain with stage of the disease

4. To look into the correlation of pain with duration of disease.

5. To analyse the correlation of pain with drugs and the response to Parkinson's treatment

REVIEW OF LITERATURE

REVIEW OF LITERATURE

SOURCE OF LITERATURE

The literature source for review of our study was taken from published studies describing the prevalence of pain, characteristics of pain and its response to treatment. Priority was given to more recent studies and older studies were used when no other data was available, Articles published in English were only used. Medline and Movement Disorder Society were the main electronic data used for the literature review.

Since there is a paucity of Indian studies on the subject, most of the literature is based on Western studies. The aim of the literature review was to fill the gaps in knowledge regarding pain in PD. The main limitations were lack of convincing studies from India regarding pain in Parkinson's Disease and its characteristics.

PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

Parkinsonism is a syndrome described by a combination of any of the six following cardinal features, tremor at rest, bradykinesia, rigidity, loss of postural reflexes, flexed posture and freezing. A combination of the symptoms are used to define definite, probable and possible parkinsonism. The most common cause is idiopathic and is known as Parkinson's Disease. The clinical complex was first described by James Parkinson in

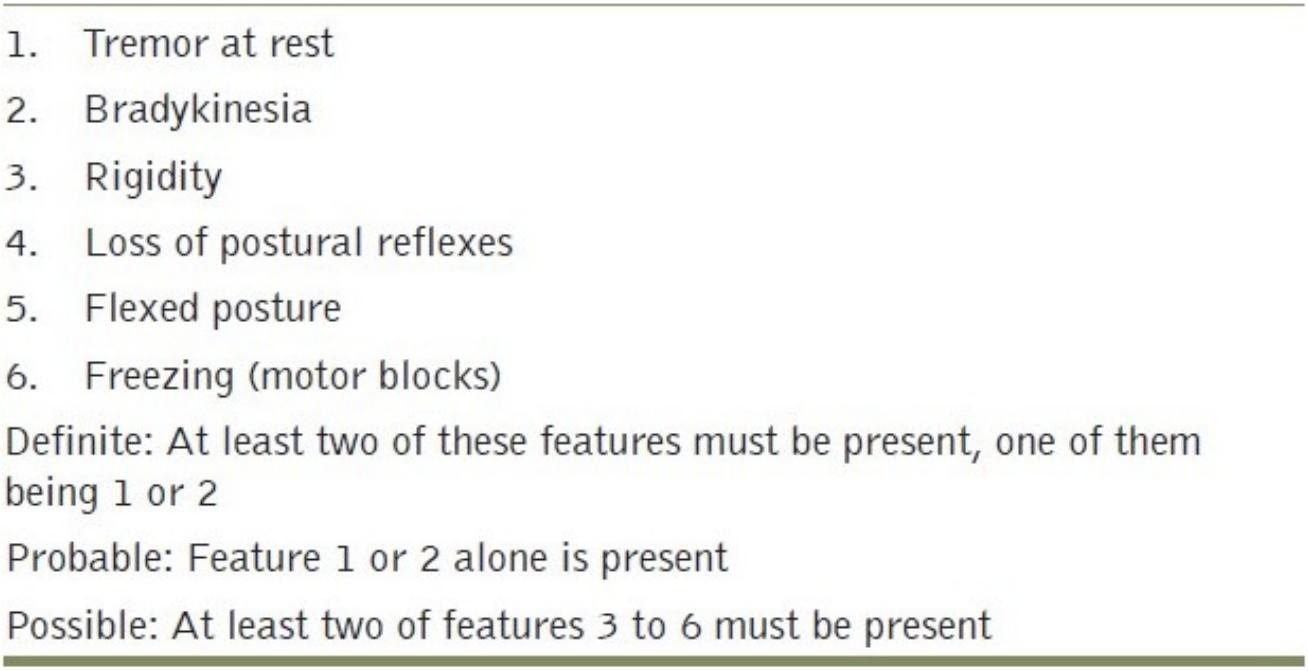


Fig 1. Parkinsonism Diagnostic Criteria[1]

1817. Parkinson's Disease was earlier referred to as "paralytic agitans" and "maladie de Parkinson" by Charcot.[1]

Parkinson's Disease is idiopathic and is a diagnosis of exclusion. The clinical diagnosis is made using the United Kingdom Parkinson's Disease Society(UKPDS) Brain Bank Criteria or the recent Movement Disorder Society- Parkinson's Disease Criteria (MDS-PD).

(Hughes AJ et al. J Neurol Neurosurg Psychiatry 1992;55:181-4)

Inclusion criteria	Exclusion criteria	Supportive criteria
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)	History of repeated strokes with stepwise progression of parkinsonian features	(Three or more required for diagnosis of definite PD)
	History of repeated head injury	Unilateral onset
	History of definite encephalitis	Rest tremor present
And at least one of the following:	Oculogyric crises	Progressive disorder
Muscular rigidity	Neuroleptic treatment at onset of symptoms	Persistent asymmetry affecting side of onset most
4-6 Hz rest tremor	More than one affected relative	Excellent response (70-100%) to levodopa
Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction	Sustained remission	Severe levodopa-induced chorea
	Strictly unilateral features after 3 yr	Levodopa response for 5 yr or more
	Supranuclear gaze palsy	Clinical course of 10 yr or more
	Cerebellar signs	
	Early severe autonomic involvement	
	Early severe dementia with disturbances of memory, language, and praxis	
	Babinski sign	
	Presence of cerebral tumour or communicating hydrocephalus on CT scan	
	Negative response to large doses of L-dopa (if malabsorption excluded)	
	MPTP exposure	

Fig 2. UKPDS Brain Bank criteria for PD

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.[30] Once parkinsonism has been diagnosed:

Diagnosis of **Clinically Established PD** requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable PD** requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

Supportive criteria
(Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
☐ 2. Presence of levodopa-induced dyskinesia
☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:

☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease
☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

Red flags

☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
☐ 3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
   a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
   b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

Fig 3. MDS- PD clinical criteria[2]

ANATOMICAL PATHOLOGY

The main site of pathology in PD is the basal ganglia, primarily the substantia nigra compacta (SN_C). SN shows depigmentation, loss of nerve cells and gliosis. Other common sites involved in the brain are the locus ceruleus and the raphe nuclei. All these cells also show depigmentation as well. Lewy bodies have been described as the primary pathological hallmark of PD. They have been found also in the peripheral nervous system and the central nervous system, including the cerebral cortex, dorsal

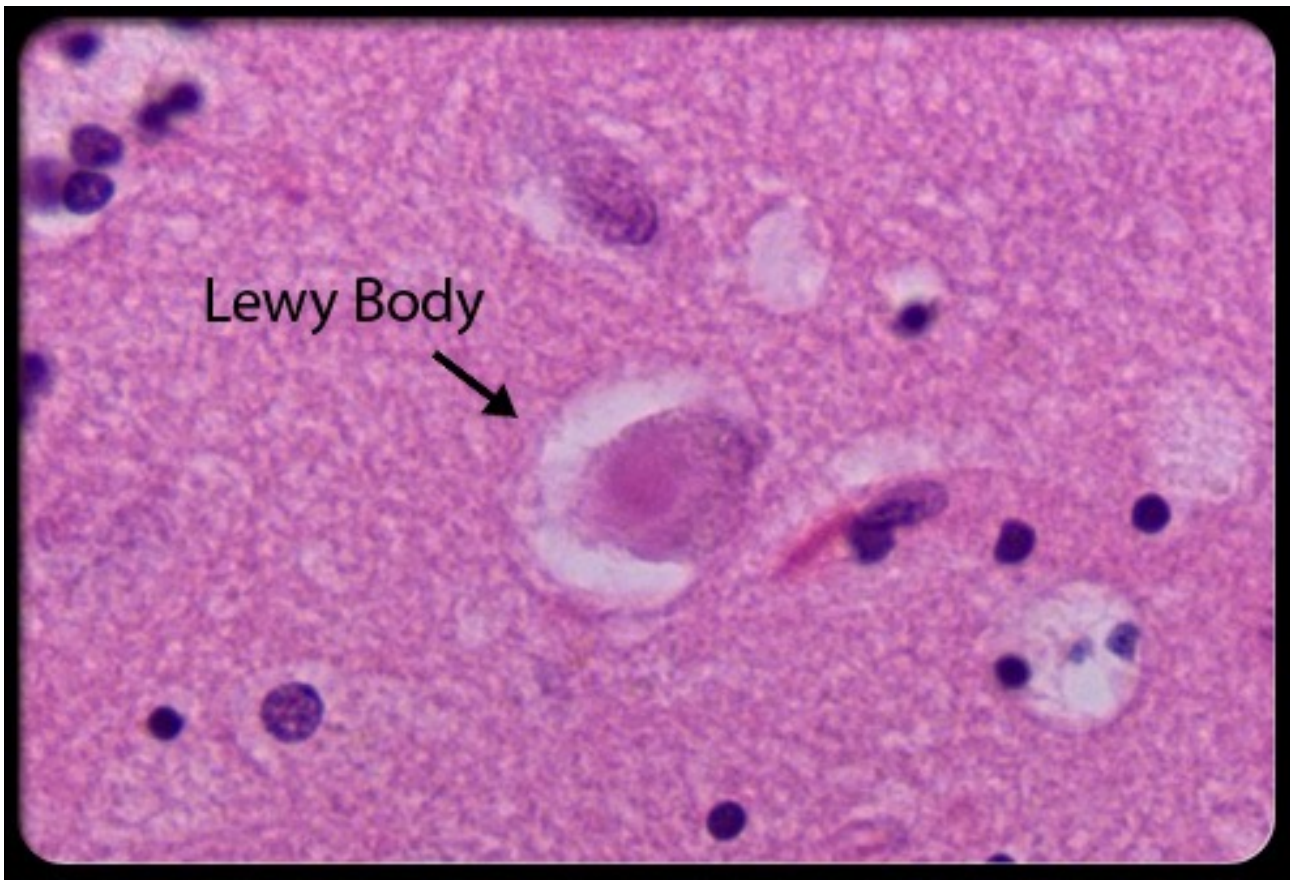


Fig.4. Lewy Bodies[3]

motor vagal nucleus, hypothalamus, nucleus basalis of Meynert and sympathetic ganglia.

The presence of Lewy Bodies helps differentiate PD from Parkinson's Plus syndromes and post-encephalitic Parkinsonism. However some of the forms of juvenile PD and mutations of parkin and LRRK2 genes are exceptions, with absence of Lewy Bodies.

Lewy bodies consist of a dense inner core surrounded by a radiating filamentous outer zone. [1]

BIOCHEMICAL PATHOLOGY

Loss of dopamine in the basal ganglia has been defined as the primary biochemical alteration in the patient with PD. Dopaminergic neurons project from the Substantia Nigra compacta to the neostriatum and from the ventral tegmental area to the limbic system and neocortex. PD spares the mesolimbic and mesocortical neurons. The nigrostriatal neurons are progressively lost. Posterior striatum, especially the putamen, is the earliest site involved. This can be picked up earliest on FDOPA PET scans.

PD also has loss of other monoaminergic neurons containing norepinephrine and serotonin. However this is to a lesser extent than dopamine. Dopamine loss accounts for most of the motor symptoms whereas the non motor symptoms are acoounted for by loss of other neurotransmitters, including acetylcholine which is decreased in the thalamus. This loss of neurons leads to hypersentivity to the neurotransmitter which leads to compensation of symptoms in early deficiency. The symptoms of PD manifest only when there is an 80% reduction in dopamine in the putamen which corresponds to a 60% loss of nigrostriatal dopaminergic neurons.

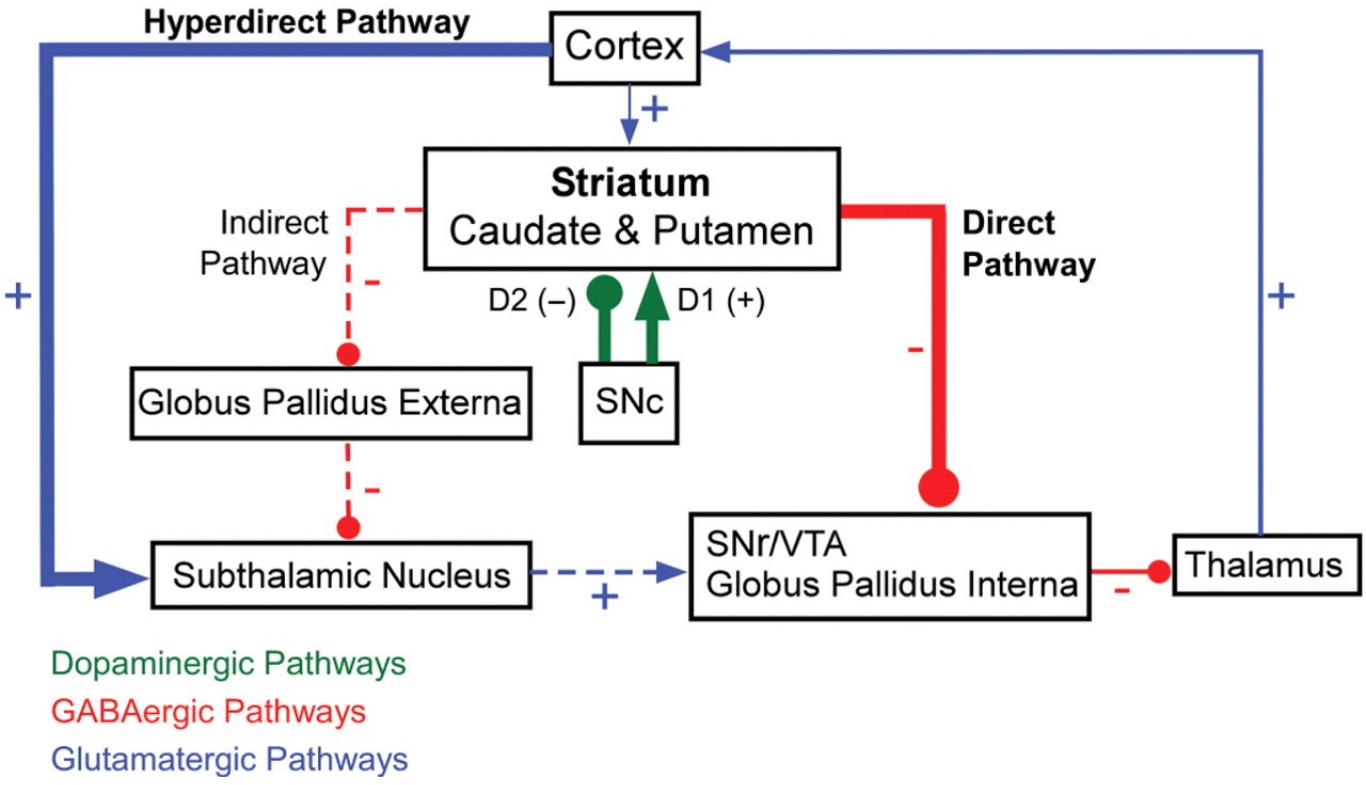


Fig.5. Pathways of Basal Ganglia[4]

The loss of dopaminergic neurons of the Substantia Nigra compacta is highly correlated to the motor symptoms of PD. Other symtpoms are not as well correlated to a specific monoaminergic neruron or neurotransmitter.

ETIOPATHOGENESIS

Multiple mechanisms of neuronal damage have been proposed in Parkinson's Disease. oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammation and apoptosis. Toxic protein accumulation, in the form of Lewy bodies and neurites, has been proposed recently to be the major pathogenic factor at play. Toxic protein accumulation can be a consequence of either impaired degradation or excessive synthesis that saturates the degradation mechanism.

Oxidative stress occurs due to monoamine metabolism and auto-oxidation. Reduced glutathione has been found consistently in PD at post mortem. However there is still debate whether the reduced glutathione is either a cause or result of excess oxidative stress. Neuromelanin is proposed to be protective against oxidative stress. Iron accumulation has been proposed to accumulate to oxidative stress. Uric acid, an endogenous antioxidant, has been found to protect against the progression of PD. This has lent credence to the oxidative stress theory of Parkinson's Disease.

Mitochondrion dysfunction is another important mechanism that is suggested in the pathogenesis of Parkinson's Disease. 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP)

intoxication causes impairment of Complex I activity in mitochondrion and dopamine neuron destruction. Rotenone is another Complex I toxin which can cause PD. Mitochodrial injury may be the consequence or the cause of Parkinson's Disease. Dysfunction leads to impaired ATP production, which in turn impairs the ubiquitin- proteasomal system. This also contributes to oxidative and nitrosative stress, which in turn leads to a vicious cycle of mitochondrial injury and oxidative injury. Mitochondria injury is also a source of free radicals, impaired calcium homeostasis and leads to initiation of cell-death via apoptotic pathways.

Glutaminergic excess, nitric oxide leading to nitrosative stress also have been shown to cause mitochondrial injury.

Genetics is now emerging as a more common etiological factor of Parkinson's Disease. Multiple genes have been implicated in pathogenesis of Parkinson's Disease and newer ones are being discovered currently.

Familial cases of PD have been recognised over the years. However since the inheritance of PD could not be reliably defined, the contribution of genetic factors was inititally discounted. However multiple familial series with autosomal

dominant inheritance and incomplete penetration have been described.

The earliest gene described was *SNCA,* which causes an autosomal dominant type of familial PD, with younger age of onset, rapid worsening and early cognitive impairment. This gene was initially labelled as *PARK1*.

Alpha-synuclein and ubiquitin are major components of Lewy bodies and mutations in the same can lead to progression of the disease.

PARK2 mutations are autosomal recessive and are prominent causes of Young-Onset Parkinson's Disease, both sporatic and familial. They lead to a slowly progressive disease with sustained response to dopamine and drug induced dyskinesias, dystonia, sleep benefit and hyperreflexia may be present.

PARK3 is considered to be a susceptibility gene since it leads to a phenotype of slow disease similar to sporadic late-onset PD.

PARK4 mutation has a varied clinical presentation from simple postural tremor to full blown Parkinson's Disease

PARK5 is an autosomal dominant mutation in ubiquitin - carboxy- terminal- hydrolase L1. This plays a part in ubiquitin-proteasomal degradation and defect of the gene can affect ubiquitin clearance leading to neuronal damage.

PINK1 gene encodes a mitochondrial serine/threonine kinase. They can resemble the parkin mutation.

PARK7 mutations are also called DJ-1 mutation. They cause a slow onset disease similar to *parkin* mutations. The DJ-1 mutation leads to oxidative stress in the basal ganglia.

PARK8 is the most common PD gene mutation. It affects protein leucine-rich repeat kinase 2 (LRRK2). It causes activation of protein kinase which in turn leads to oxidative stress and damage.

PARK9 is a gene defect seen in Parkinson Plus Disorders, which is transmitted in an autosomal recessive pattern.

Multiple named syndromes have been reported to be associated with PD, namely Gaucher's, Perry syndrome and Infantile dystonia-Parkinsonism.

Recently an in-utero mechanism of dopamine loss has been postulated in which in-utero or perinatal insult leads to loss of dopaminergic neurons. The transcription factors for the various stages of dopamine production have been proposed as the target molecules. This correlates to the pathological finding of decreased number of dopaminergic neurons in the patients with infantile parkinsonism.

STAGING OF PARKINSON'S DISEASE

The staging of Parkinson's Disease is highly important for planning the treatment program. However the primarily importance of staging is for research purposes. The staging can be either clinical or pathological.

PATHOLOGICAL STAGING

The pathological staging of Parkinson's Disease is known as Braak Staging and was described by Heiko Braak in 2003. It was derived based on post-mortem analysis of brain matter of patients with diagnosed idiopathic Parkinson's Disease. He described that the intracerebral formation of Lewy inclusion bodies and Lewy neurites has a topographically predictable

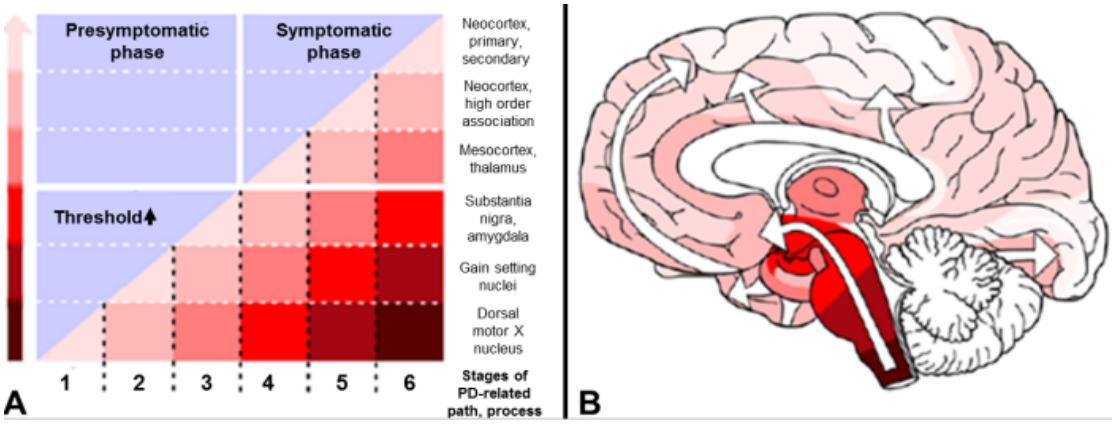


Fig.6. Braak Pathological staging of Parkinson's disease

progression. There are 6 stages defined with 1,2,&3 usually

being presymptomatic PD while stages 3,4,5,&6 are symptomatic.[5]

The stages as described are :

1. Stage 1 (Medulla Oblongata)

Lesions are initially see in the dorsal glossopharyngeal/vagal motor nucleus and int he anterior olfactory nucleus. This explains why some pre-symptomatic PD patients have loss of smell. Lewy bodies in the enteric nervous system has also been seen in this stage. This explains why pre-symptomatic PD patients have gastrointestinal symptoms. The olfactory pathology does not spread into the surrounding regions whereas the lesions in the brainstem may expand upwards.

2. Stage 2 (Medulla oblongata + pontine tegmentum)

Here the lesions are also present in caudal raphe nuclei, gigantocellular reticular nucleus and coeruleus-subcoeruleus complex.

3. Stage 3 (Midbrain)

The pathology extends to midbrain, particularly the pars compacta of the Substantia Nigra

4. Stage 4 (basal prosencephalon and mesocortex)

The lesions extend to prosencephalon and cortical involvement confined to the temporal mesocortex (transentorhinal region) and allocortex (CA2- plexus) with sparing of the neocortex.

5. Stage 5 (Neocortex)

Neocortical involvement in the form of high order sensory association areas and the prefrontal neocortex.

6. Stage 6 (Neocortex)

Pathology of the stage 5 regions along with first order sensory association areas of the neocortex and premotor areas, with occasional changes in primary sensory and motor areas.[5]

The pathological stages can be predicted using FDOPA- PET scanning and is useful for early diagnosis of the disease and thus leading to earlier intervention

CLINICAL STAGING

The clinical staging is much more important than the pathological staging since it is much more useful in prognostication and predicting the course of disease.

The commonly used staging system is the Hoehn and Yahr staging system. The system was first proposed by Melvin Yahr and Margaret Yoehn in 1967 in the journal *Neurology*. There are 5 stages in the originally proposed staging and it was expanded with stages 1.5 and 2.5 later in the modified staging.

Stage	Definition
1	Unilateral Disease
2	Bilateral disease with recovery on the pull test
3	Mild to moderate bilateral disease with postural instability; physically independent
4	Severe disability; still able to walk or stand independently
5	Wheelchair bound or unless aided

Fig.7. Hoehn And Yahr Staging[7]

The clinical staging is based on the symmetricity of the symptoms and the severity of the functional motor impairment [8]

Hoehn and Yahr scale	Modified Hoehn and Yahr scale
1: Unilateral involvement only usually with minimal or no functional disability	1.0: Unilateral involvement only
	1.5: Unilateral and axial involvement
2: Bilateral or midline involvement without impairment of balance	2.0: Bilateral involvement without impairment of balance
	2.5: Mild bilateral disease with recovery on pull test
3: Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent[a]	3.0: Mild to moderate bilateral disease; some postural instability; physically independent
4: Severely disabling disease; still able to walk or stand unassisted	4.0: Severe disability; still able to walk or stand unassisted
5: Confinement to bed or wheelchair unless aided	5.0: Wheelchair bound or bedridden unless aided

[a]Stage 3 is a summary of the authors' original, more narrative description.

Fig.8. Comparison of Hoehn and Yahr and Modified Hoehn and Yahr scale

The Hoehn and Yahr scale is used as the reference standard for testing newly developed scales of impairment in Parkinson's Disease. The stage correlates significantly with the quality of life as measured by other standard scales. However it is related inconsistently to other scales such as self care scales and the Webster score. The HY scale also predicts the time of progression of the disease from one stage to the next. However in recent times the use of levodopa has altered the rate of progression and impaired prediction of disease progression. Recently FDOPA PET scan of dopaminergic activity in the brain has been found to correlate well with the Hoehn and Yahr stage. All these have led to Hoehn and Yahr scale being the most widely used and accepted staging system for Parkinson's Disease.

There are a few limitations of this scale however. The scale does not differentiate between impairment and disability,i.e., it does not differentiate between the subjective and objective components of the disease. And due to its insistence on laterality of the symptoms, a severe unilateral disability can still be under staged. The Hoehn and Yahr staging has only five stages and hence the small progressions in disease cannot be made out. Each stage is broadly classified and is not clearly defined by a set clinical/ radiological test. It is highly subjective and still does not have a specific stepwise testing program for classification. Hoehn and Yahr also does not take into account the non-motor symptoms of Parkinson's Disease. However despite these drawbacks, Hoehn and Yahr staging still remains the most useful clinical staging system in use.[8]

PAIN IN PARKINSON'S DISEASE

Pain is an important and distressing symptom of Parkinson's Disease. It is a well recognised and common non-motor symptom. James Parkinson had initially decribed that "painful symptoms can be the first sign of impairment".[9] The type of pain which is present is usually classified for diagnostic purposes into the following:

1. Musculoskeletal pain
2. Radicular/ neuropathic
3. Dystonia- related
4. Akathitic discomfort
5. Central/ primary Parkinsonian pain[9]

PATHOPHYSIOLOGY OF PAIN IN PARKINSON'S DISEASE

The exact pathophysiology of pain in Parkinson's Disease has not yet been delineated. Multiple mechanisms are described but there is no consensus about which is the primary pathologic mechanism.

Abnormal somatosensory processing by the basal ganglia has been proposed. This involves the substantia nigra, caudate, putamen, globus pallidus, thalamus and their connections. It has

been proposed that basal ganglia act as a gating centre for nociceptive stimuli within the striatum and limbic system before the nociceptive stimuli are relayed to the neocortex for perception.

Dopamine has also been shown to raise the pain threshold. Absence of dopamine will lead to lowering of the threshold and increased and widespread stimulation of the somatosensory cortex in response to pain.

The medial spinoreticulothalamic tract contains slow conducting fibres that transmit pain from the pain receptors to the somatosensory cortex. The tract projects to the medullary core and the mesencephalon. It synapses in the parabrachium, nucleus gigantocellularis, hypothalamus and periaqueductal grey matter, intralaminar and medial thalamic nuclei, insula, parietal operculum, anterior cingulate cortex, amygdala and hippocampus. This pathway subserves the autonomic, affective and cognitive components of pain. The nucleus parabarachial locus ceruleus and the periaqueductal grey are sites of Lewy body deposition in Parkinson's Disease. This explains the altered pain sensation and perception in Parkinson's Disease.[9]

Parkinson's Disease patients have also demonstrated a diminished pain or nociceptive pain reflex (NFR) threshold as

well as abnormalities in evoked brain potentials and sympathetic skin response (SSR) on electrophysiologic testing. [10] Additionally, new evidence has emerged that central vegetative centres also play a role in nociceptive disturbances. [10] There are inconsistencies in the studies reported about differences in the pathway of pain. Some studies have reported electrophysiological nociceptive disturbances only in patients with Parkinson's Disease who experience central pain. Other studies revealed that the electrophysiological nociceptive abnormalities did not respond to dopaminergic drugs. This argues against dopamine deficiency being the underlying pathology of pain in Parkinson's Disease. [10]

The ambiguous nature of these studies can be explained by the fact that most of the studies have been based only on a single level of pain testing and does not test across multiple levels of the Central Nervous System, i.e., spinal, subcortical-vegetative, cortical , subjective. The psychophysiological parameter of the nociceptive system which are usually tested are the Nociceptive Flexion Reflex, which tests the spinal level, pain-evoked brain potentials, which test the cortical level, and subjective rating scales, which test only the subjective component of the pain. Multiple-method studies are needed to describe the conribution

of each component of the pain pathway to the nociceptive abnormalities detected in Parkinson's Disease. This also helps to differentiate the abnormalities in the afferent and efferent pathways of the nociceptive system.[10]

Additionally a "three-loop" pathway has been proposed for the processing of pain and other non-motor symptoms in Parkinson's Disease. Rodent models have shown that D1-mediated pathways between insular cortex and basal ganglia, are crucial in mediating the descending inhibition of pain. The antinociceptive activity has been shown to be dependent on D2 receptors within the striatum and right medial temporal cortex in healthy individuals.[11] This plays a role in the altered pain perception in patients suffering from Parkinson's Disease.

One study combined two method testing ,using Laser-evoked brain potentials (LEP) and sympathetic skin responses (SSR), to evaluate two different sites of pain perception. This study had different responses during the On and Off durations of the Parkinson's Disease during treatment. In the Off period, there were increased Laser-evoked brain potentials and lack of habituation to Sympathetic Skin responses. This was reversed in the On period. This led the authors of the study to propose that afferent sensitisation of the pain pathways leads to the

increased Laser-evoked brain potentials and abnormal vegetative nociceptive processing in the brainstem regions can dampen the habituation of Sympathetic Skin Responses.[10] This has led to a postulation that abnomrnal over-activity of the autonomic nervous system occurs in response to nociceptive stimuli in patients with Parkinson's Disease who suffer central pain.

Dopamine deficiency has demonstrated an amplification intrastriatally of sensory inputs from corticostriatal projections. This leads to an amplification of perceived painful sensations leading to hyperalgesia. This mechanism is especially important in central Parkinsonian pain but may extend to other types of pain perceived in Parkinson's Disease. [11]

Laser evoked Brain Potentials have shown reduced N2/P2 potentials bilaterally, compared to controls, in patients with Parkinson's Disease, even if only hemiparkinson. It was affected only on side of symptoms in patients not started on treatment. The administration of levodopa was not found to alter these amplitudes. The heat-pain threshold was found to be lower in patients with Parkinson's disease when compared to controls. The decrease was more on the side of the body with severe symptoms. Even within this group, the threshold was

much lower for patients suffering from pain when compared to those who were not. There was a difference in the N2/P2 amplitude in different types of pain with muscular pain having a decreased amplitude and the central Parkinsonian pain showing an increased amplitude. These differences can be due to differences in the pathophysiology of the different types of pain. However differences in methodology used, such as the technique, number of averaged stimuli and duration of interstimulus interval are all considerations that must be taken into account before validating such findings. The greater reduction in N2/P2 amplitude in patients with pain in Parkinson's Disease need not always be an additional change in the pain processing pathways in this population, but can be the result of something called the "segmental inhibitory effect".

A study by J.A. Priebe et al [10] combined three levels of pain processing in testing for abnormalities. The study used a multi-method approach to test spinal, subcortical- vegetative and cortical levels. The study revealed starkly contrasting results on spinal and vegetative levels. The heat pain threshold was decreased in the Off period, but not in the On period. This led to the conclusion that dopaminergic drugs can raise the heat-pain threshold. However abnormalities of the vegetative

parameters is seen in both periods. The spinal and cortical parameters showed only minor dysfunctions compared to the vegetative parameters. This study also showed no significant correlation between the experimental parameters and the disease duration or motor symptom severity as measured by United Kingdom Parkinson's Disease Rating Scale.[10]

This study also revealed absence of abnormalities in the peripheral A- delta fibres and spinothalamic tract, the central ascending nociceptive pathways, in Parkinson's Disease patients. This was in contrast to previous studies which showed abnormalities of cortical pain processing. The abnormalities in cortical pain processing was, however, found to correlate well with the advances of motor symptoms and stage of the disease. [10]

The study also revealed that the relationship between the amplitude of evoked brain potentials and pain ratings of the eliciting stimuli was altered in patients with Parkinson's Disease. This points to abnormalities of the dopaminergic cortical-basal ganglia- thalamic- cortical loop.[10]

However it has been shown that only dopaminergic pathways are affected and the subjective perception of pain in Parkinson's Disease remain unaltered when they are modulated

by adrenergic, serotonergic and opiodergic mechanisms in experimental models. These pathways constitute the usual descending inhibitory nociceptive controls.[11] The modulating effect of noradrenergic and serotonergic systems on descending pain pathways has been suggested to be affected in patients with Parkinson's Disease in a few studies. This is supported by the significant correlation of pain and depression in patients with Parkinson's Disease. The ameliorative effect of duloxetine on central pain also supports this hypothesis.

Anomalies of glutamate metabolism, in the form of excessive activation of group III metabotropic receptors, has been shown to affect nociception peripherally and result in neuropathic pain in animal models.

Other neurotransmitters such as N-methyl-D-aspartate, adrenaline and GABA have been implicated in the modulation of pain pathway in the basal ganglia. The proposed mechanism has been an upregulation in NMDA receptors adn Alpha-2 adrenoceptors which play a role in modulation of the sensory pathways in the basal ganglia with sparing of the motor pathways.

Functional studies also have provided evidence to confirm the abnormal central processing of pain. PET scans during the Off-

phase showed increased pain-induced cortical activation, in the form of increased regional cerebral blood flow, which was reversed in the On-phase. However this has not correlated significantly with increase in pain threshold in patients on administration of levodopa and other dopaminergic agents.[15] The areas which showed activation were the insula/SII, which is involved in discriminative pain processing and the anterior cingulate cortex and the prefrontal cortex, which function as affective processing areas of pain.[17] Patients with pain also had lower pain activation in right prefrontal cortex and posterior insula while higher pain activation was seen in the right anterior cingulate cortex. Levodopa was shown to reduce the response to pain stimulus in the posterior insula and anterior cingulate cortexin patients with Parkinson's Disease without pain. This effect could not be replicated by apomorphine.[17] This has led to the possibility that levodopa may induce its anti-nociceptive effects through a mechanism other than the increase of dopamine in the central nervous system.

The effect of levodopa on the pain thresholds is not yet comprehensively elucidated. A rise in the cold-pain threshold is seen , but the degree of rise depends on the underlying disease process. Patients with dyskinesis and fluctuations tend to have

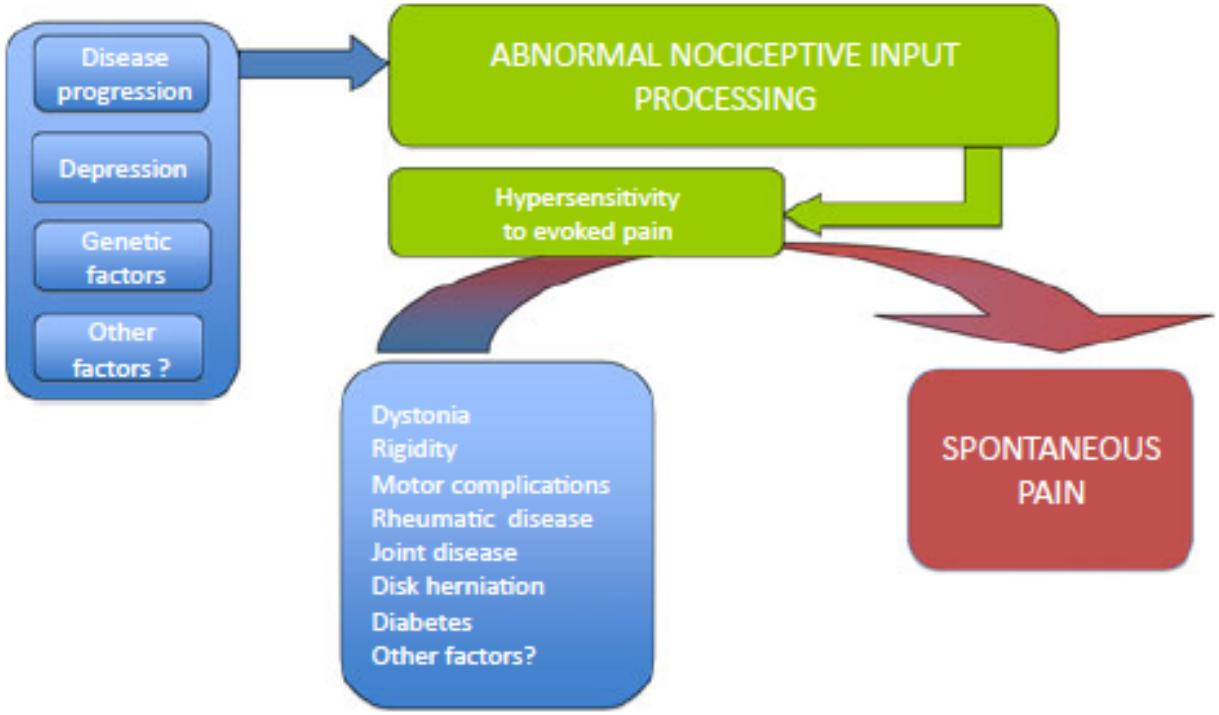


Fig.9. Factors and mechanisms of Pain in Parkinson's Disease[17]

a much greater rise in threshold compared to non-fluctuators.[17] Most of the studies including pain response to levodopa were done on subject populations with longer duration of disease, and hence would include patients with treatment associated complications such as fluctuations and dyskinesias. This factor has not been mentioned in some of the studies showing a positive response to levodopa, but should be taken into consideration when analysing the results.

Some neurosurgical studies after Deep Brain Stimulation have also supported the role of basal ganglia in modulation of pain. Pallidotomy or Globus Pallidus stimulation by Deep Brain

Stimulation (either unilateral or bilateral), has demonstrated a subjective improvement in Parkinson's Disease related pain.[15]

Animal studies have also supported the role of basal ganglia in pain processing. Caudate, putamen and globus pallidus have show distinct responses to thermal stimulation in rats. Lesioning and microinjection of somatostatin in the caudate and putamen in animal models has shown an anaesthetic effect.[15]

One study showed no differences in descending nociceptive inhibitory control system activation among patients with Parkinson's Disease with pain, with variable types and qualities of pain when compared to those without pain. This argues against the involvement of this system in Parkinson's Disease.[17]

A review of studies on the pathophysiology of pain reported that only mild changes in pain-processing mechanisms are seen and this contributes to the intermittent type of pain seen in patients with Parkinson's Disease. The studies have returned a lack of correlation between the degree of lowering of pain threshold and the severity and intensity of the pain experienced by the patient. However this does not reflect a mutual exclusion between abnormalities of pain processing pathways and the

spontaneous pain experienced in patients suffering from pain in Parkinson's Disease.[17]

All these findings point towards increased activity in both the ascending lateral and medial pain pathways. The abnormalities in pain processing have also been found in patients with Parkinson's Disease which points to an underlying process that predisposes patients to spontaneous pain but additional factors are necessary for the pain to manifest. These factors have been proposed to be the possible risk factors associated with higher prevalence of pain. These include female gender, severe motor complications and other coexisting painful medical conditions. The association of a single genetic variant with multiple pain types has also led to the belief that the background abnormal nociceptive processing changes are the same in all patients with pain in Parkinson's Disease, regardless of the type of pain experienced.[17] Except for central pain, all the other types of pain ,ay develop on this background abnormalities based on the coexisting medical conditions and motor complications.

PREVALENCE OF PAIN IN PARKINSON'S DISEASE

Various studies have reported varying prevalence of pain in Parkinson's Disease. This had revealed a wide range from 40% up to 83%.[11] Almost 40% of patients with Parkinson's Disease complain of painful symptoms in one study.[9] Pain has also been considered a premotor symptom of the disease. One study reported pain in upto 25% of patients before treatment and upto 40% of all Parkinson's Disease patients in the early stages of disease.

A British study revealed PD-related pain to be responsive to dopaminergic drugs, prominent on the side of motor symptoms. Most patients suffered from two concomitant pain syndromes in 85%, whereas pain indirectly related to Parkinson's Disease was 1% and pain related to Parkinson's treatment was 8%. The non-Parkinson's Disease related pain was found to be constantly more severe.[12] The number of pains was not found to increase with the stage of the disease. The severity of pain was found to correlate to the presence of depression and other non-motor symptoms. The "blind spot" in this study was the fact that Parkinson's Disease patients with severely impaired cognitive function could not be adequately assessed regarding the

Study Type	Pain Type	Study	PD Sample Size	Prevalence (%)
Controlled studies	All pain types	Ehrt et al. (2009)[52]	227	67 PD versus 39 controls
		Defazio et al. (2008)[10]	402	69.9 PD versus 62.8 controls
		Negre-Pages et al. (2008)[12]	450	61.8 PD chronic pain; twice more frequent in PD than in patients without PD
		Chaudhuri et al. (2006)[48]	123	27.6 PD versus 30.2 controls
		Quittenbaum and Grahn (2004)[47]	57	68.4 PD pain in past month; similar to control
	Shoulder pain	Madden and Hall (2010)[23]	25	80 PD versus 40 controls
	Back pain	Broetz et al. (2007)[49]	101	74 PD versus 24 controls
		Etchepare et al. (2006)[93]	104	59.6 PD versus 23 controls
	Sensory symptoms	Snider et al. (1976)[94]	101	43 PD versus 8 controls
Uncontrolled studies	All pain types	Hanagasi et al. (2011)[55]	96	64.9
		Santos-Garcia et al. (2011)[53]	159	72.3
		Chaudhuri et al. (2010)[7]	242	45.9
		Beiske et al. (2009)[21]	176	83
		Martinez-Martin et al. (2007)[95]	545	28.8
		Sullivan et al. (2007)[96]	100	35
		Lee et al. (2006)[46]	123	85
		Tinazzi et al. (2006)[28]	117	40
		Giuffrida et al. (2005)[97]	388	67
	Pain "directly related to PD"	Letro et al. (2009)[54]	50	54
		Goetz et al. (1986)[50]	95	46
	Shoulder pain	Stamey et al. (2008)[9]	309	35
	Burning mouth	Clifford et al. (1998)[44]	115	24

Fig.10. Prevalence of Pain in Parkinson's Disease[15]

presence, severity or type of pain. The pain was most frequently found to be intermittent and periodic. The most common location of pain was the proximal extremities, with most patients complaining of a cramping, aching or feeling of tightness in the proximal limbs. Only a small fraction of the study population (4.9%) were found to have Parkinson's Disease related neuropathic pain. This was in contrast to other preceding studies such as Snider et al. who reported higher fraction of neuropathic pain (11%). However this study included not just patients with Parkinson's Disease, but also patients with post-encephalitic Parkinsonism, who were more likely to have sensory abnormalities. This can account for the increased prevalence of neuropathic pain in this study.[12] The

British study has another drawback in that it did not have a control group to compare results with. A background prevalence of pain in the elderly population has been estimated at 70 %[12] . However in this study the prevalence of pain in Parkinson's Disease was found to be higher at 85%. A model of "background" non- Parkinson's Disease related pain with a "superimposed" pain of Parkinson's Disease was proposed.[12] An age-matched controlled trial would be needed to prove this model. The pain was also reported to be a dominant factor in the quality of life of almost 50% of these patients.

Another study in French out-patients, showed that chronic pain was found in 60% of patients, of which 60% was related to the disease and 40% was unrelated.[13]

A Norwegian study revealed Parkinson's Disease related pain in 83%, musculoskeletal pain in 70%, dystonic pain in 40%, radicular pain in 20% and central pain in 10%.[14]

Chronic pain has also led to development or aggravation of depressive symptoms, more commonly in elderly individuals. In a Norwegian study, 67% had pain and this incidence correlated with higher severity of depression. This also closely correlated with higher degree of motor impairment and more cognitive impairment and longer duration of the disease. However this

study could not prove a direct causality between depression and pain in patients with Parkinson's Disease. [14]

Pain in Parkinson's Disease is associated with a poorer quality of life. Pain is ranked high among the disabling symptoms in Parkinson's Disease in all stages of the disease. In the early stages, it ranks as the most disabling non-motor symptom only secondary to the cardinal motor symptoms of slowing, tremor and stiffness. In later stages of the disease it ranked sixth on the list of most disabling symptoms. Despite these findings, it still remains unrecognised or undeclared in almost 40% of patients with Parkinson's Disease. [15]

Some patients with Parkinson's Disease complain of multiple types of pain. In one study, two different types of pain were seen in 24% and three types were reported in 5%. The most common site of pain reported in the study was the back at 74%. In the study among outpatients, a substantial proportion (46%) attributed their pain directly directly to the presence of Parkinson's Disease.[15] However, since this is highly subjective and the cause of pain cannot be easily differentiated, further large-scale, controlled studies are needed to eliminate subjective bias.

The presence of pain was reported in some studies to be significantly associated with female gender, younger age of onset of disease , disease severity and depression. However these findings have been inconsistent and negative correlations have been demonstrated in other studies.[15] The cause for this discrepancy could be the small sample size, non-representative study population or self rating data collection which remains highly subjective.[15]

One other factor proposed to be associated with Parkinson's Disease related pain is pre-existing medical conditions such as diabetes mellitus, osteroporosis, rheumatic disease , degenerative joint and disc disease and arthritis. A genetic component of the predisposition to pain has also been recently proposed. The genes in question are variants in SCN9A and FAAH genes.[17]

A systematic review of prevalence study by Broen et al. using modified QUADAS tool shed more light onto the characteristics of pain. This review reported that the prevalence varied across 8 studies from 40% to 85% with a weighted average of 67.6%. This wide variability was could be explained by methodological disparities, difficulties in clear cut definition of chronic pain and inability to distinguish Parkinson's Disease related and

unrelated pain and a selection bias due to most of these studies being in tertiary care centres. Parkinson's Disease related pain was reported in 3 studies with a prevalence of 57.6%. Pain in the lower limbs was reported as the most frequent at 47.2%. Back pain was seen in 14.3% , pain in the upper limbs was 13.8% and neck and shoulder pain was seen in 12.4%.[16] The pain in the lower limbs is more likely to be neuropathic Among the types of pain from the studies, musculoskeletal pain was the most common in 46.4% of all Parkinson's Disease patients and 55.6% of patients with Parkinson's Disease related pain. Next in prevalence was dystonic pain in 19.6%, radicular pain in 9.1% and central pain in 5.6%. Akathisia was reported inconsistently and could not be definitively described. It was assumed that this only consisted of a minority of patients with pain in Parkinson's Disease.[16] Pain frequency is usually proportional to severity of motor signs and symptoms. However pain can manifest independent of motor problems in 25-64% of patients with Parkinson's Disease.[17]

SYMPATHETIC SKIN RESPONSE (SSR)

The sympathetic skin response is a response to pain mediated via the medial pain system.The impulse is carried by A-delta fibres to the spinothalamic tract and carried upward to the medial thalamic nuclei. From this , afferents are given to the anterior cingulate cortex and the higher cortical centres such as the insula and the somatosensory cortex. An efferent from the anterior cingulate cortex projects to the anterior hypothalamus, which in turn produces the Sympathetic Skin Response via further relays in the brainstem, vegetative centres and post-ganglionic C- fibres. In patients with Parkinson's Disease, the efferent pathways in this reflex are affected since they contain the vegetative nuclei. These nuclei, especially the periaqueductal gray matter (PAG), contain dopaminergic neurons which can be affected in Parkinson's Disease. One more fact to be taken into account at this juncture is that the pathology of Parkinson's Disease starts in the brainstem and ascends upwards. Hence the periaqueductal gray matter is affected early in the course of the disease, as determined by Braak staging. This accounts for the minimal pain abnormalities detected in the study by J.A. Priebe et al in patients with early stages of Parkinson's Disease.[10] The Lamina I of the dorsal horn

of the spinal cord has shown aggregation of Lewy Bodies in Parkinson's Disease. This can contribute to the increased temporal summation of sensory stimuli and decreasing the nociceptive stimulus threshold at the spinal level. [11] However this has not correlated with the intensity, quality or distribution of muscular or neuropathic pain.

NOCICEPTIVE FLEXION RESPONSE (NFR) & LASER EVOKED BRAIN POTENTIALS (LEP)

This is a motor action in response to a painful stimulus. The Nociceptive Flexion Response is a spinal level test of pain of modulation and perception. It depends on an intact afferent pathway of A- delta fibres to the dorsal horn and an intact efferent pathway through spinal circuits. These pathways have a top- down control from the thalamus via brainstem and an inhibitory effect from the substantia nigra to the thalamus and brainstem,i.e., the medial pain pathway. This is altered in Parkinson's Disease, leading to a decreased pain threshold to Nociceptive Flexion Response, along with increased amplitudes of the response. This points towards a spinal segment disturbance in nociception. This alteration in Nociceptive Flexion Response threshold has been showed to be responsive

to dopaminergic drugs such as levodopa.[10] The lack of descending inhibition of pain can also contribute to referred pain and secondary hyperalgesia. [11] The nociceptive spinal response is the earliest abnormality of pain perception detected in Parkinson's Disease. It may be abnormal even when the subjective assessment of provoke pain remains unaltered. The abnormality of the nociceptive flexion response correlates with the presence of musculoskeletal pain due to abnormal pain processing in the spinal cord. The involvement of the medial pain pathway can be demonstrated early by PET scans. This does not correlate with the severity, intensity, quality or distribution of pain. Both the nociceptive flexion response and laser-evoked brain potentials were found to have lowered thresholds even in patients with Parkinson's Disease who did not have pain. [17] However using a lower number of averaged stimuli and longer interstimulus intervals has recorded normal Laser-evoked brain potentials in patients with Parkinson's Disease who do not suffer from pain. Hence the methodology used is also of prime importance in testing.[17]

Levodopa intake, acutely, has shown increase in the Nociceptive flexion response threshold, even in patients with Parkinson's Disease without pain. This was disputed in a later

study. Levodopa also had no effect on the N2/P2 amplitudes. The threshold for Nociceptive flexion response was found to be inversely related to the severity of motor signs. No such relationship was found for N2/P2 anplitude lowering.

ROLE OF PHASE (ON/OFF)

Most of the parameters have shown insignificant differences in the pain testing during the two phases. Only the heat-pain threshold has shown the pattern of being abnormally low in the Off phase which was reversed in the On phase. This points against an effective response of pain to dopaminergic drugs. This lack of difference in downregulation of Sympathetic Skin Reflex has been explained by three proposed mechanism:

1. The stimulation of the basal ganglia by medication is not sufficient to provide adequate activity of the Periaqueductal Gray matter, which is essential for Sympathetic Skin Reflex.
2. The degeneration of the Autonomic Nervous System in the form of cholinergic post- ganglionic sympathetic fibres attenuates this reflex.
3. The vegetative level of pain perception depends on other neurotransmitters, the loss of which in Parkinson's Disease is not replaced by dopaminergic treatment.

The hypersensitivity to pain is usually higher in the Off period and is amenable to treatment with dopaminergic agents. In some patients though, paradoxical decrease in pain perception has been reported in the Off phase. This contradiction can be explained by the theory that Off period also worsens motor impairment, which results in decreased facial expression of the perceived pain, which can improve with treatment.[10]

A systematic analysis of studies has shown a significant improvement of the pain after dopaminergic drugs was seen only in 28.6%. Broetz et al. found no correlation between pain and the duration in the Off phase. This lack of association led to the hypothesis that other mechanisms might also underlie pain.[16]

CLINICAL PAIN SYNDROMES

Pain in a patient with Parkinson's Disease should be considered along with other cardinal symptoms of PD. The painful symptoms may be exacerbated, relieved or not altered by PD treatment. This is an important history that should be always questioned in patients complaining of pain.

Ford initially classified pain in Parkinson's Disease into 5 types:[12]

1. Musculoskeletal pain due to Parkinsonian rigidity or musculoskeletal abnormalities
2. Radicular- neuropathic pain due to a root or peripheral neurve lesion
3. Dystonic pain related to anti-Parkinsonian medications
4. Central or primary pain related to dopaminergic drug dosing and timing
5. Akathisia, which can be drug induced or related to Off periods

Another scheme of classification of pain in Parkinson's Disease was proposed by Serratrice and Michel in 1999.[12] The pain was classified into two headings:

1. Primary pain syndromes- directly related to Parkinson's Disease such as cramps or paresthesia
2. Secondary pain syndromes- postural disorders osteoarthritis,etc.

Dystonic pain is diagnosed when the pain presents with writhing, cramping or posturing of a body part.

Akathisia refers to an intensely unpleasant sensation that need not be painful but merely uncomfortable.

Primary Parkinsonian pain is suspected to be a central pain occurring due to defective modulation of the pain pathways. This is unrelated to the motor symptoms and is diagnosed partly

Types of Pain/Discomfort	Features
Musculoskeletal	Aching, cramping pain, frozen shoulder, back pain May be caused by parkinsonian rigidity, immobility, and mechanical factors Associated rheumatologic and orthopedic disease
Dystonic	Dystonic posturing and spasms Levodopa-induced dystonia: wearing off dystonia or morning dystonia, peak-dose dystonia, diphasic dystonia
Neuropathic	Radicular neuropathic: Localized to a specific nerve root distribution of dermatome Probably not directly related to PD Peripheral neuropathic: Symmetrical, distal
Central	Poorly localized Boring, constant, burning Vague sensations of tension and discomfort Visceral and autonomic discomfort[a]
Akathitic discomfort	Inner restlessness, urge to move
Others	Oral and genital pain: Burning mouth or vagina syndrome May represent a sensory wearing off and may improve with levodopa[a]

[a]May be considered a nonmotor "off" symptom.

Fig.11. Classification of pain in Parkinson's Disease[15]

on the clinical presentation and partly by exclusion of other causes of pain.

The pain in PD has been found to improve with medications for Parkinsonism. This has led to grouping of variation of pain along with non-motor complications. The fluctuation may also be due to fluctuation of the motor tone in skeletal muscles that characteristically occurs in PD.[9]

Myofascial pain syndrome is another common type of pain seen in almost 79% of patients with pain in Parkinson's Disease. This poses a diagnostic challenge since the pain is usually a referred pain due to a secondary hyperalgesia and is spatially distant from affected muscles.[11]

The classification of pain in Parkinson's Disease according to the above mentioned systems is difficult due to a significant amount of overlap between the different described pain syndromes. The lack of clear objective measures and the incomplete understanding of the mechanism of the pain syndromes also contributes to the confusion. A newer updated classification was proposed by Ha, Jankovic et al., which included other pain syndromes such as peripheral neuropathic pain and oral and genital pain[15].

MUSCULOSKELETAL PAIN

Aching ,cramping and joint pains have been described in PD very commonly. The prevalence of musculoskeletal pain in Parkinson's Disease has been reported to be as high as 70%.[15] This type of pain is probably related to the increased tone, rigidity, abnormal posturing and stiffness of muscles. The cramping is more common in the neck, arm and calf while the joint aches are more common in the shoulder, hips , knees and ankles. This pain increases during long periods of Parkinsonian symptoms. Hence, in theory, the pain should respond to anti-Parkinsonian medication, unless contractures have formed.[9] The pain may be the presenting symptom of PD. For example, frozen shoulder has been reported not infrequently as the presenting symptom of Parkinson's Disease. The excessive contractures can lead to a stooped posture known as camptocormia. Shoulder pain may be the initial presentation of Parkinson's Disease, even before the onset of motor symptoms.This symptom correlated significantly with the side of subsequent maximal motor severity. A marked limitation of movements of the shoulder joint with decreased range of movements and localised pain, known as "frozen shoulder", is a common finding in

Parkinson's Disease. The patients with Parkinson's Disease were found to have a 21- times higher chance of suffering from frozen shoulder compared to age and sex matched controls. Supraspinatus tear, subcoracoid effusion and acromioclavicular joint changes have been demonstrated on MRI, which correlated well with UPDRS scores. Rheumatic arthritis is a close differential diagnosis, since the findings of joint involvement and pain will mimic it. The classical pattern of involvement in Parkinson's Disease is flexion of the metacarpophalangeal joints and distal interphalangeal joints with extension of the proximal interphalangeal joint, with ulnar deviation.[15] These findings are called "striatal hand and foot" and "pseudorheumatoid deformities". These findings can be reliably differentiated from rheumatoid arthritis by the characteristic absence of inflammatory changes in the joints and the unilaterality of the findings.[15] Patients with muscular pain were also found to have reduced N2/P2 amplitudes on stimulation with CO2 for Laser Evoked brain Potentials. This has led to the suggestion that muscular pain also has a central component.[15]

RADICULAR/ NEURITIC PAIN

Radicular pain is seen in 14% of patients with PD who complain of pain.[9] There might be paresthetic sensations such as coolness, numbness, tingling, etc., which might be mistaken for central pain or sensory symptoms. The prevalence in one study was around 20%.[15] These must be always tested for compressive root or peripheral nerve injury which needs focused management. Peripheral nerve involvement can also occur as a part of the pathological process of Parkinson's Disease. Alpha-synuclein accumulation within the sensory afferents has been demonstrated. Levodopa administration is believed to interfere with cobalamin metabolism in the peripheral nervous system. This can lead to elevated methylmalonic acid[15] .Both these mechanisms can contribute to neuropathic pain which is due to peripheral neuropathy in patients with Parkinson's Disease.[11] The muscular rigidity of spinal muscles can also leads to abnormalities in the vertebral column and intervertebral discs. This can give rise to radicular pain, which typically manifests as low back pain. [11] In contrast to other types of pain in Parkinson's Disease, the laser-evoked brain potentials are decreased in amplitude in patients with radicular or peripheral neuropathic pain. Abnormal joint position sense has also been

reported in some patients with Parkinson's Disease.[15] Neurodegeneration of nociceptors has been found as an early feature of Parkinson's Disease. Skin biopsies showed reduced nerve fibres and Meissner's corpuscles, with a decrease in unmyelinated nerve fibre density.[15]

DYSTONIC PAIN

A diagnosis of dystonic pain is made when patient complains of pain and has dystonia in the form of abnormal cramping, twisting or posturing of a limb or other body part. The prevalence was reported to be around 40%.[15] The pain characteristically responds to dopaminergic treatment and the timing of the pain is classically early in the morning before taking drugs or late in the day, during the wearing off effect of the drugs. The dystonia can be severe enough to cause joint dislocation, commonly at the shoulder.

The early morning pain can be relieved by levodopa or be severe enough to require subcutaneous apomorphine injections. The dystonia may be relived by botulinum toxin injections and deep brain stimulation of the Subthalamic Nucleus or the Globus Pallidus Interna. However paradoxically, deep brain

stimulation can also cause exacerbation of the pain due to stimulation of the internal capsule.[9]

The dyskinesia associated pain has been shown to be the most amenable to palliation by dopaminergic drugs. The pain threshold was found to be reduced in the off period of patients with dyskinesias. The involvement of the limbic cortex and other associated structures, especially the reward system, has been postulated. The overactivity of these structures in Parkinson's Disease can lead to abnormal pain perception. [11] Dopaminergic projections from the ventral tegmentum to the nucleus accumbens, which constitutes the mesolimbic pain inhibitory pathway, can be involved in Parkinson's Disease. This again leads to disinhibition of pain pathway activation and leads to increased nociception. [11]

Dystonia, especially involving the feet, may be the presenting symptom of Parkinson's Disease. This is more commonly seen in Young-onset Parkinson's Disease, especially when associated with the *Parkin* gene mutation. In other patients, dystonia more commonly occurs a complication of dopaminergic treatment. This type of dystonia can present at various stages of the medication cycle including the following:

1. Early morning, off-medication- seen in 15%

2. Diphasic dystonia
3. Peak dose dystonia

AKATHISIA

Akathisia refers to an inner restlessness which is a common and potentially disabling symptom of Parkinson's Disease. This leads to an inability to remain still, with a constant urge to keep moving. This was seen in around 45% of patients suffering from Parkinson's Disease.[15]This needs to be distinguished from other conditions such as dyskinesias, anxiety and depression. The primary pathology is a dopamine defect in the mesocortical pathway.

The symptom responds in about 50% of patients to increase in dopaminergic dosing.[9] Akathisia needs to be managed properly since it might be severe enough to impair the activities of daily living.

Akathisia correlates with the severity and age of onset of Parkinson's Disease. It has been misdiagnosed as Restless Leg Syndrome, which is another sensory-motor disorder which can occur in Parkinson's Disease. The two conditions can be differentiated based on the characteristics of Restless Leg Syndrome, which is "an urge to move the legs, particularly at

night", as opposed to generalised restlssness as seen in akathisia.[15]

CENTRAL PAIN

Central Parkinsonian pain is defined as pain as part of the disease per se , and not due to dystonia, nerve injury or musculoskeletal pain. It was initially described by Souques in 1921[9]. The prevalence in one study was reported to be around 10%.[15] The location of abnormal pain syndromes are head, neck, epigastrium, abdomen, genitalia, face , pharynx, pelvis or rectum, These are sites where neuropathy or dystonia are less likely to occur. The pain may have different characteristics but usually are distressing, relentless and obsessional that may overshadow other symptoms of Parkinsonism. The pain may respond sometimes to dopaminergic treatment. If it does , the character of the pain is usually visceral or autonomic in origin. It fluctuates according to the drug levels in the serum. In those who the pain does not respond to dopaminergic drugs, conventional anti pain medications may be tried. However the effectiveness of the drugs is not definite. The pain can characteristically be described as "poorly localised, constant, boring, ineffable, not limited to a dermatome or neural

distribution".[15] This central pain syndrome can also be seen in other diseases of the central nervous system such as stroke, myelopathies and multiple sclerosis. Central pain was found in one study to correlate with Off-period non-motor symptoms, with the attendant fluctuations with treatment.[15] Oral and genital burning pain can occur in patients with Parkinson's Disease. This is usually considered a tardive syndrome of the disease.[15]

PAIN SCALE

There are multiple scales available for quantifying pain. However almost all of them are subjective with the objective scales still in development.

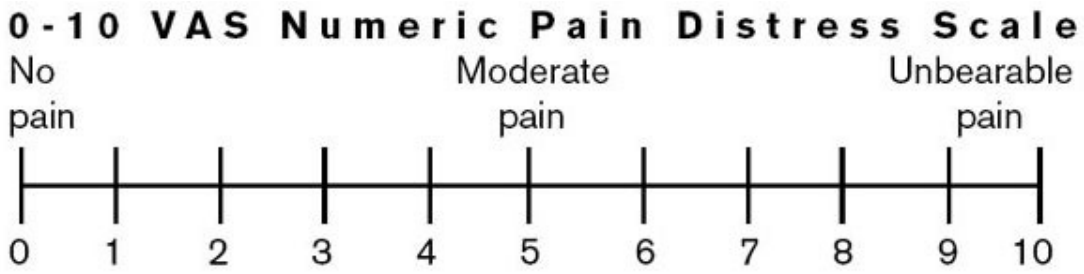


Fig12.Visual Analog Pain Scale

Visual Analog Scale is a psychometric response scale which is relatively easy to administer. The patient is asked to scale their level of agreement

with the administered question along a continuum from least agreement to most agreement. This helps to quantify a highly subjective variable such as pain into more discrete values.

There are other scales to assess pain in Parkinson's Disease such as:

1. UPDRS Part- II, item 17 (sensory symptoms)
2. Brief Pain Inventory
3. McGill Pain Questionnaire (MPQ)
4. Douleur Neuropathique (DN-4)
5. PainDETECT
6. Neuropathic Pain Symptoms Inventory

The visual analog scale remains the most commonly used scale to quantify pain in Parkinson's Disease due to its ease of administration.[11] The Visual Analog Scale is useful but cannot well characterise intermittent pain, as seen in patients with the On-Off fluctuations of pain.

The UPDRS scale does not provide information on the type of pain and hence does not help in the classification of pain and decision on treatment.[11]

The short form of the Brief Pain Inventory has been found to be effective in quantifying the intensity of pain and its impact on activities of daily living. This has found use in patients with Parkinson's Disease.

The McGill Pain Questionnaire helps in differntially quantifying the different aspects of pain such as sensory-discriminative, affective and evaluative. This differentiation has been useful in pointing out difference in pain response to various treatment modalities.

Douleur Neuropathique measures only neuropathic pain, along with PainDETECT and Neuropathic Pain Systems Inventory. It is not sensitive for the other types of pain. However the Douleur Neuropathique has a very high sensitivity and specificity for the diagnosis and quantification of neuropathic pain.

The Neuropathic Pain Systems Inventory is helpful in the follow up of the neuropathic pain and also helps to characterise the pain according to the clustering of symptoms into spontaneous, evoked or paroxysmal pain.[11]

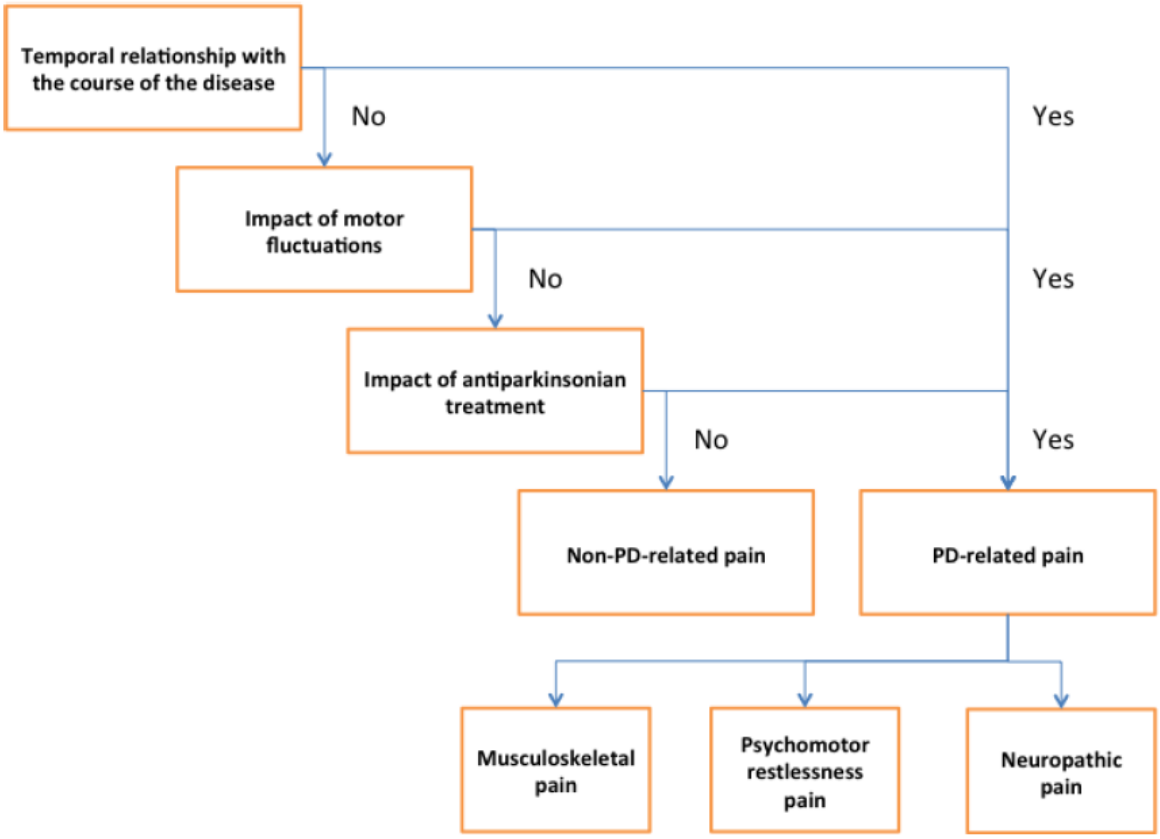


Fig.13. Taxonomy of Pain according to Marburg-Sao-Paulo-Creteil Questionnaire for Pain in Parkinson's Disease[11]

The importance of the different aspects of pain was shown in a study, which tested response of pain to SubThalamic Nucleus-Deep Brain Stimulation (STN-DBS). This showed an improvement in the sensory and affective aspects of pain, and not the evaluative, post surgery. This study also showed a more robust improvement in musculoskeletal pain when compared to neuropathic pain, in patients with Parkinson's Disease.[11]

The assessment of pain in Parkinson's Disease needs to take into account multiple variables so as to avoid bias. The motor

status of the patient, the treatment given (medical or surgical) and its complications (off stage / dyskinesias) must all be noted.

The timing of pain and its association with the motor and non-motor status of the patient helps to link the pain to Parkinson's Disease. Given the high prevalence of chronic pain syndromes in older age groups, in whom Parkinson's Disease is most prevalent, these factors help in establishing a connection between the pain and Parkinson's Disease.

There are a couple of questionnaires in development for the study of pain in Parkinson's Disease. One is being developed by the non-motor study group of the International Parkinson and Movement Disorder Society. Another is the "Marburg- Sao Paulo- Creteil Questionnaire for Pain in Parkinson's Disease".[11] This takes into account three important variables:

1. Temporal association of onset of pain and Parkinson's Disease symptoms, excluding other causes
2. Dependence of pain on motor fluctuations
3. Dependence of pain on anti-Parkinsonian treatment

COGNITION AND PAIN

Cognitive functions in the general population have been found to be inversely related to pain. Executive functioning and attention are the domains more commonly studied to correlate with pain. Processing of pain shows significant overlap with an attention-specific network, affecting attention. The degree of affection correlates with the severity of the pain. A higher MMSE (Mini Mental State Examination) was shown to correlate with a better pain tolerance and higher thresholds. This can be explained by the ability to centrally integrate the multiple facets of pain.

In patients with Parkinson's Disease, neocortical regions are involved late in the stage of disease and this can be associated with decrease in pain. However the fact that patients with severe cognitive impairment have difficulty in expressing and communicating their pain, this confounding factor must be taken into account.

Both impaired cognition and pain are non-motor symptoms of Parkinson's Disease. Hence the interaction between them becomes significant in planning the treatment strategy of the patients.

In a study by Engels et al., the findings were contrary to the hypothesis proposesd above. Cognitive function showed no correlation with pain. However mood disorders strongly influenced the pain response and the presence and severity of spontaneous pain in patients with Parkinson's Disease.

This absence of correlation might be attributed to the fact that neural functional reorganisation occurs in patients with cognitive impairment, such that the areas of cognitive executive processing in these patients is different from those in normal individuals. The alteration of executive function leads to lack of overlap with pain processing areas . This pheonomenon is also seen in Multiple Sclerosis. Functional studies in Parkinson's Disease have concluded that there is hyperconnectivity early in the disease and hypoconnectivity as the disease progresses with cognitive impairment, Chronic pain also can cause loss of gray matter from pain areas such as anterior cingulate cortex and insula. This may be a compensatory mechanism. Both these findings can explain the lack of correlation of pain and cognition in Parkinson's Disease. In contrast, anxiety and depression were highly predictive of pain. This correlation could be bidirectional and

can lead to a continuous feedback mechanism of pain and mood disorders. [18]

TREATMENT OF PAIN

The adequate management of pain should start with an accurate classification of the type and characteristics of the patient. Based on these, a few basic principles of treatment have been proposed. Pain associated with Off phase and fluctuations of the motor symptoms should be treated to eliminate these fluctuations.[11] This should consist of:

1. Long-lasting levodopa formulations for early morning and nocturnal akinesis.
2. Catecholamine- O- methyl transferase inhibitors, along with shortening of dose intervals of levodopa for end-of-dose akinesis.
3. Dystonic pain, more commonly seen in the Off period, and of high severity, are to be managed with long-acting levodopa in the evenings and fast-acting formulations in the early morning.
4. Rotigotine transdermal patches used once a day also has a protective effect on fluctuations and improves sleep quality.

Subthalamic Nucleus- Deep Brain Stimulation has been shown to have an effect on pain, independent of its effect on motor symptoms.[11] It has been found to relieve pain in 40%-80% of Parkinson's Disease patients post-surgically. The correlation of effect on pain and motor impairment seems to vary depending on the type of pain. This modality of treatment was found to have a maximal effect on dystonic pain which characteristically occurs in the Off drug period. This correlated with improvement in the quality of life.[11] Deep Brain Stimulation of the Globus Pallidus Interna has also been found to be effective in relieving pain in Parkinson's Disease. One study showed improvement in pain by 74% and dysesthesia by 100% following unilateral pallidal deep brain stimulation. On bilateral pallidal stimulation , this response was 90% for pain and 88% for dysesthesias. Pallidotomy has also been found to improve muscle pain in patients with Parkinson's Disease. [15]

It has been demonstrated that dopamine agonists such as apomorphine have a much lesser effect on pain, compared to levodopa. Rotigotine has been suggested as an exception to this since it improved Likert pain scale scores in the RECOVER study.[15]

Musculoskeletal pain can be managed with exercise and rehabilitative programs to correct the gait and improve the function of axial muscles, which are the primarily affected muscles in Parkinson's Disease.

Muscular deformities such as striatal foot and hand are much less responsive to dopaminergic medication. In these situations, baclofen, anticholinergic therapy and benzodiazepines have been found to be moderately successful. Botulinum toxin is another option for focal dystonias.[15]

Neuropathic pain can be managed similar to neuropathic pain of any other cause. Duloxetine , a selective serotonin and noradrenaline reuptake inhibitor, is found to be effective.

This drug has also been found to be effective in the central pain syndrome of Parkinson's Disease.

Akathisia has been found to respond to dopaminergic drugs in a few studies.

Newer strategies are now under development, which target the descending inhibitory pain control pathways. [11]

The treatment of disabling pain with analgesics was reported in a British study.[12] Almost half the patients suffering from intermittent pain did not take any analgesics owing to the periodicity of the symptom. However taking into account

patients suffering from higher severity of pain or pain which was interfering with activities of daily living, this number dropped to 20%. This study further states that pain in Parkinson's Disease is grossly undertreated.[12] This low number of patients taking analgesic medication could also be due to a possibility that the patient had taken analgesics and found them to be ineffective and hence discontinued. This history is usually missed unless specifically asked for.[16]

A systematic review of studies , 52.4% of the patients used analgesic medication. Non-opioid analgesics were used by 37.6%, weak or strong opioids by 13.5% and co-analgesics by 11.8%. The co-analgesics used were mainly anti-depressant or anti-convulsive drugs.[16]

Along with the central pain processing anomalies, treatment should also be directed to the loco-regional factors, such as rigidity, bradykinesia, osteoporosis, rheumatic disease, degenerative disc disease, arthritis and disc herniation, which contribute to the development of pain in the pain-predisposed condition that is Parkinson's Disease.[17]

MATERIALS AND METHODS

MATERIALS AND METHODS

SETTING

The study was conducted in the Madras Institute of Neurology and the Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital.

ETHICS COMMITTEE APPROVAL

The study was approved by the Institutional Ethics Committee of Madras Medical College, Chennai.

STUDY DURATION

This study was done between April 2016 and August 2016.

STUDY POPULATION

Patients with Parkinson's disease attending the Movement Disorders Clinic, Madras Institute of Neurology and patients who were admitted in the Madras Institute of Neurology and the Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital were included in the study.

TYPE OF STUDY

Observational study

SAMPLE SIZE

51 patients were recruited from the Movement Disorders Clinic, Madras Institute of Neurology and the Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital.

INCLUSION CRITERIA

Patients who were diagnosed with Parkinson's Disease according to the UKPDS Brain bank criteria.

EXCLUSION CRITERIA

Patients with a diagnosis of any of the following,

1. Psychiatric illness
2. Peripheral Neuropathy
3. Radiculopathy
4. Recent trauma
5. Parkinson Plus syndromes
6. Secondary Parkinsonism
7. Osteoarthritis

were excluded from the study.

DATA COLLECTION AND METHODS

51 Patients diagnosed with Parkinson's Disease (as defined by UKPDS Brain bank guidelines) were recruited from the Movement Disorders Clinic, Madras Institute of Neurology and the Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital.

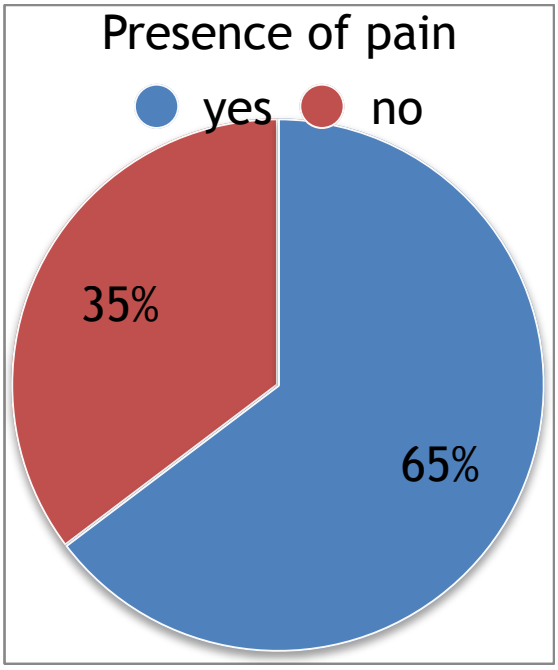
The patients were informed of the nature of the study and informed consent was obtained. The patients were categorised based on the duration and stage of the disease according to Hoehn and Yahr staging. The exclusion criteria were ruled out by history and clinical examination. The treatment history of each patient was noted. Each patient was administered a structured questionnaire. The questionnaire was administered in a standardised manner by the principal investigator. It included questions about the presence or absence of pain, along with the characteristics and severity of the pain when present. The severity of pain experienced by the patient was graded on the Visual Analog Scale. The correlation of the pain to drug intake was also noted. The questionnaire administered for the purpose of this study is included in the Annexure A.

The data collected was compiled and analysed using Excel data analysis software.

RESULTS

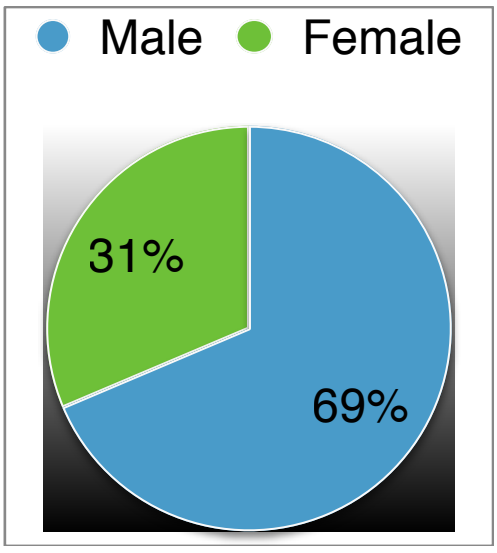
RESULTS

The total number of patients diagnosed with Parkinson's disease who satisfied the inclusion and exclusion criteria was 51. Pain was seen in 33 patients and absent in 18.

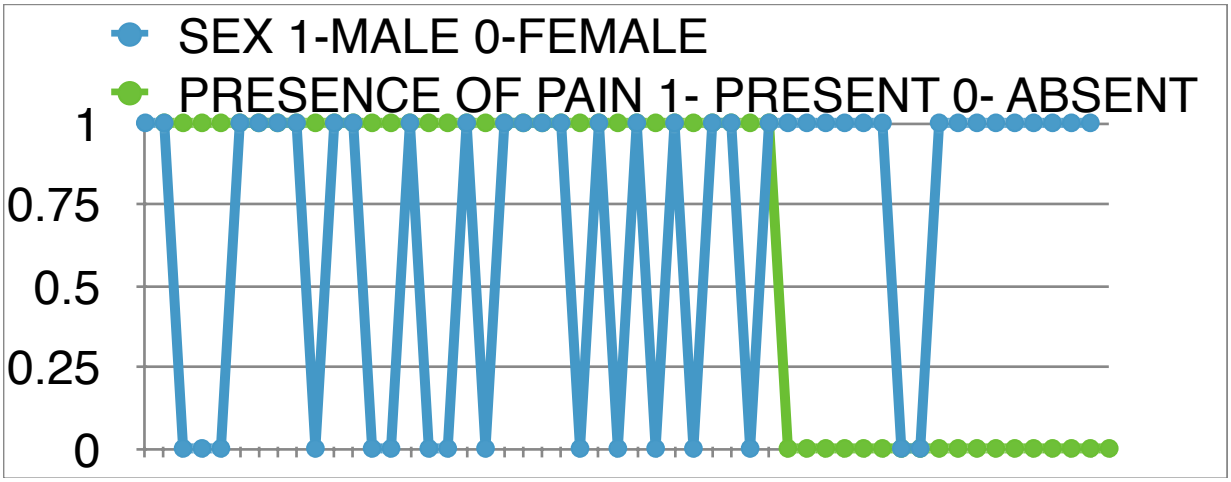


Demographic characteristics of the sample:

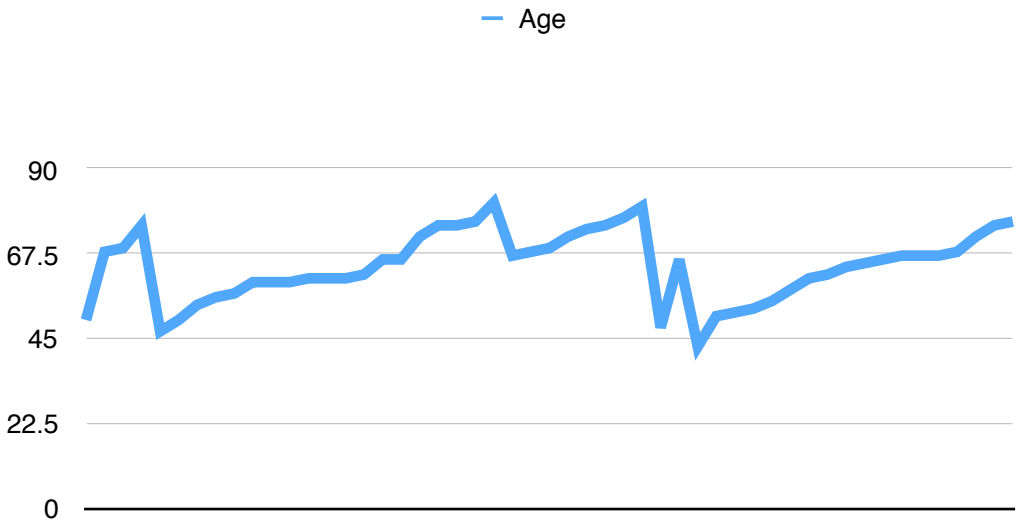
Among the patients included in the sample, there were 35 males (69%) and 16 females (31%).



The correlation between male sex and presence of pain was calculated and the R value was-0.3225. Although this shows a



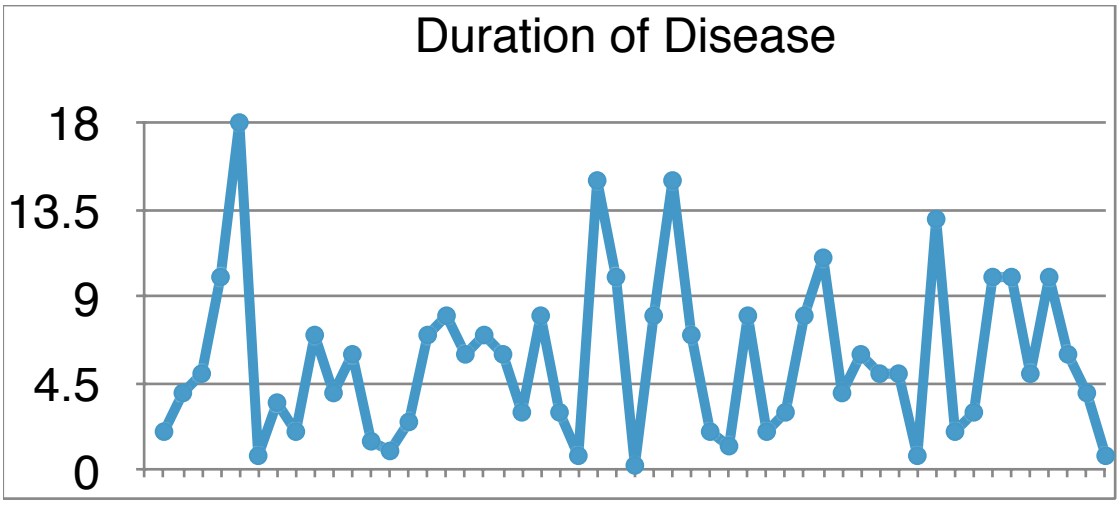
negative correlation, the relationship between the variables is weak and hence not a significant finding.



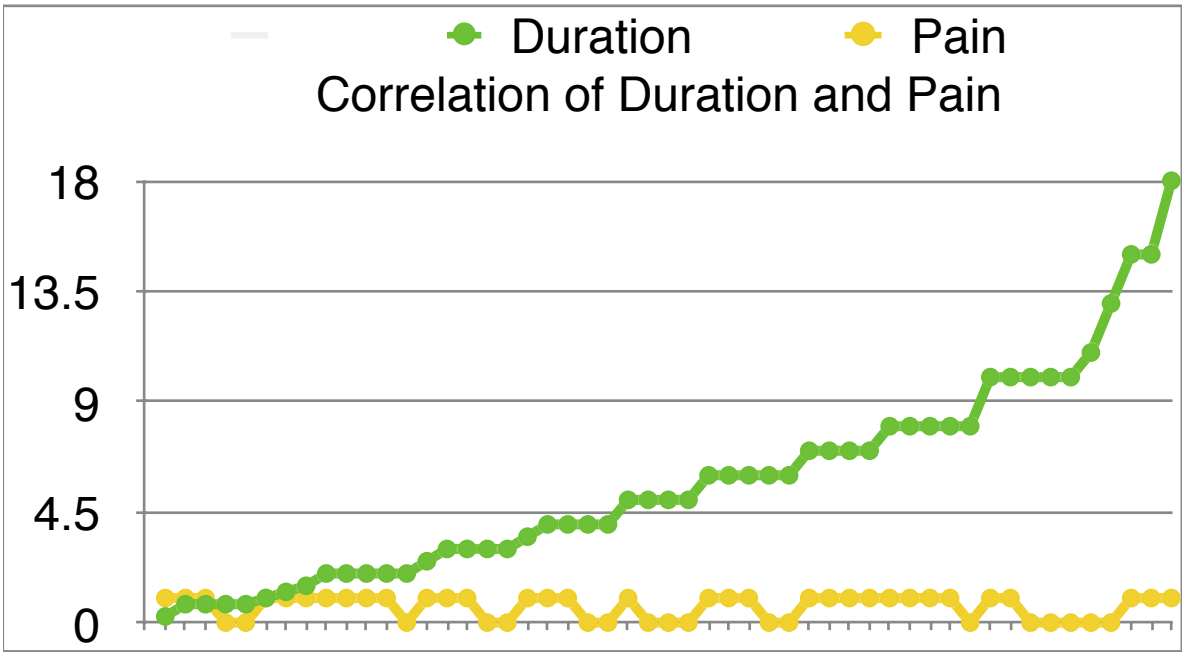
The age of the patients included in the sample ranged from 43 years of age to 81 years of age (Mean= 64.31 years ±9.25)

Disease characteristics observed in the sample:

The average duration since onset of symptoms in the sample was 5.71 years (S.D.= ±4.11).

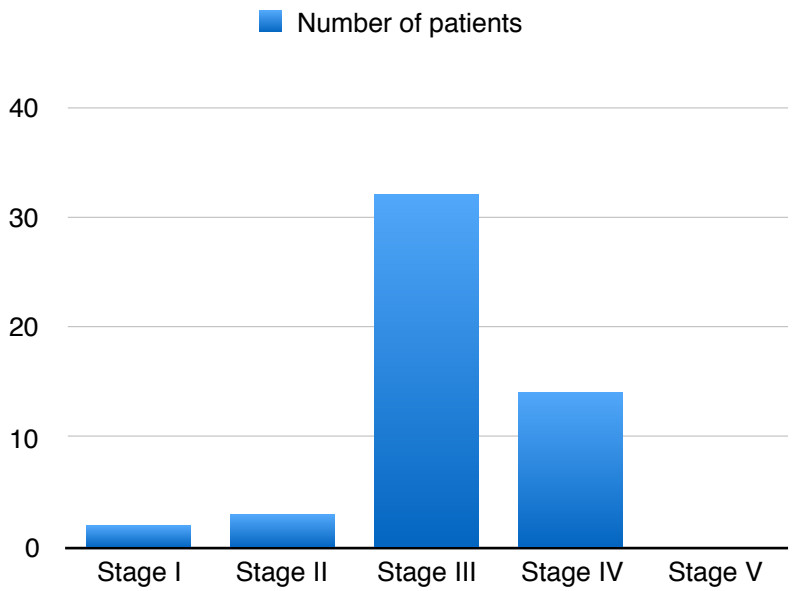


The duration of disease did not have any significant effect on pain experienced by the patient. The effect of duration of the disease on the pain experienced by the patient was not found to be statistically significant. (p= 0.4998). The correlation was R=0.3749 which was positive but not statistically significant.



Using the Hoehn and Yahr staging criteria, the stage of the disease was determined for all the patients in the sample based on the disease characteristics. There were 14 patients in stage 4

(27.45%), 32 patients in stage 3 (62.75%), 3 patients in stage 2 (5.88%) and 2 in stage 1 (3.92%).



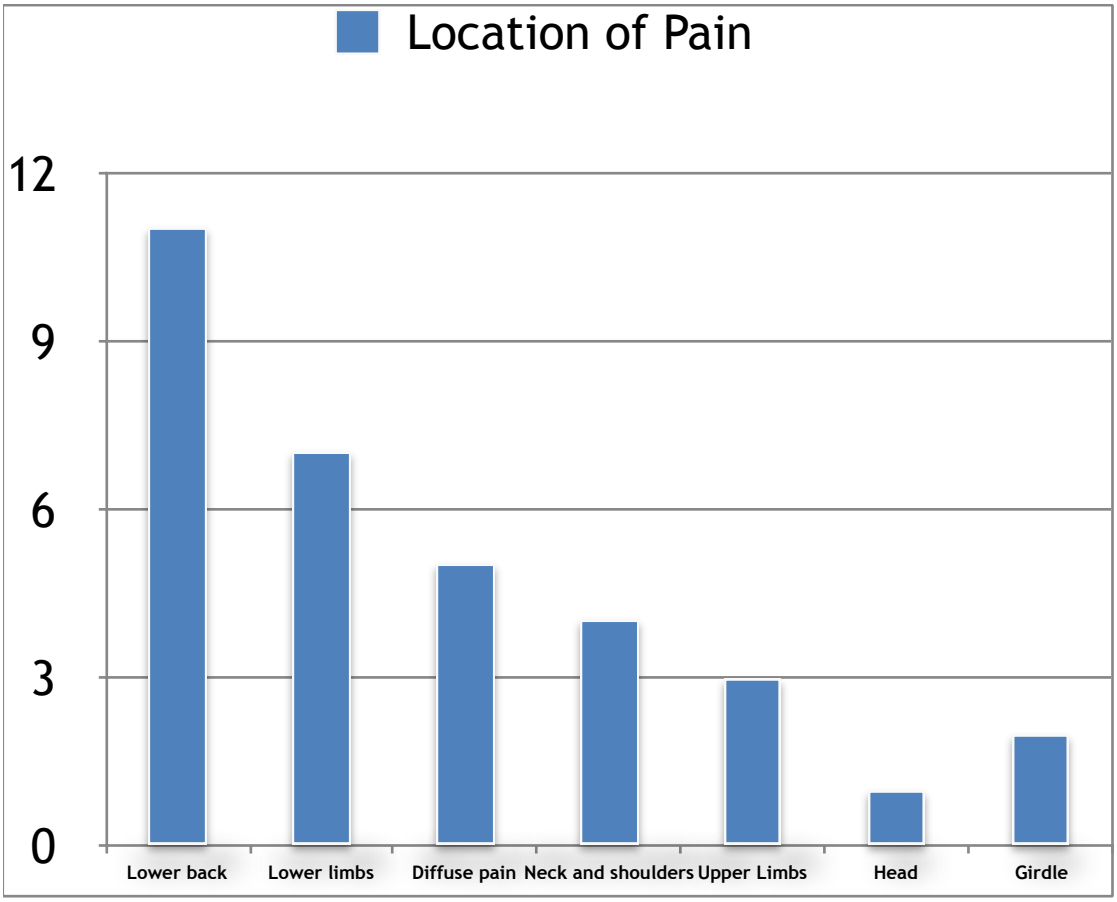
In the sample studied, 33 patients complained of pain, while 18 did not.

Localisation of the pain:

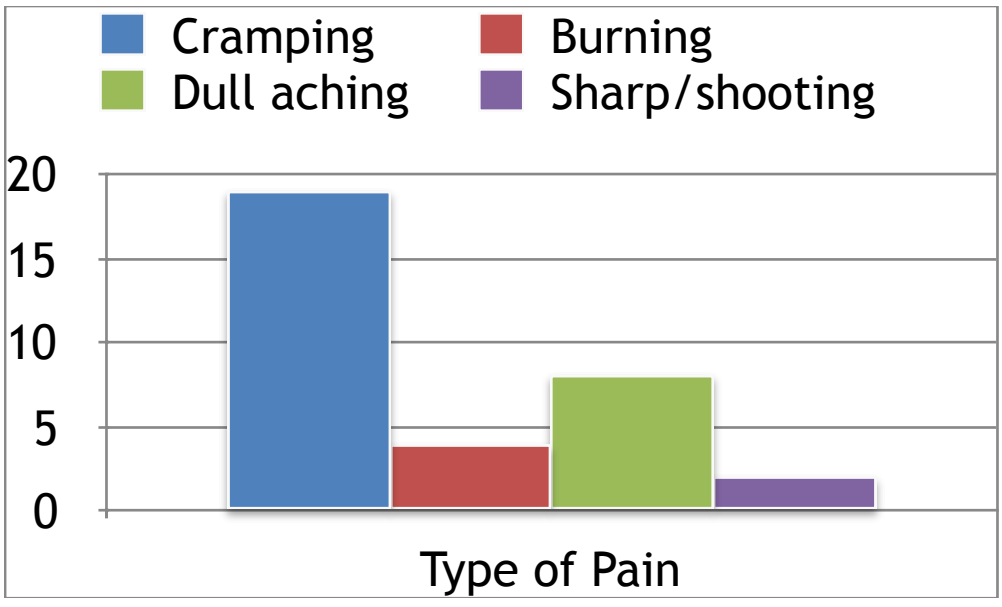
The location of the pain in the sample studied was determined based on the questionnaire. There were varied responses. The lower back was the most common site of pain (11), followed by lower limbs (7), diffuse pain (5), neck and shoulders (4), upper limbs (3), girdle (2) and head (1).

Character of Pain:

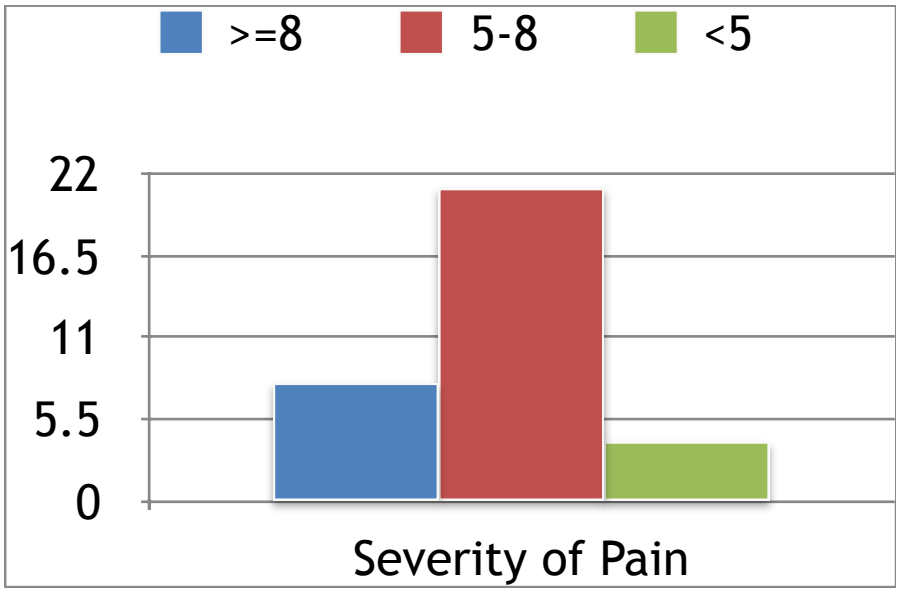
The patients in the sample complained of a varied character of pain. Of the different types, cramping was the most common



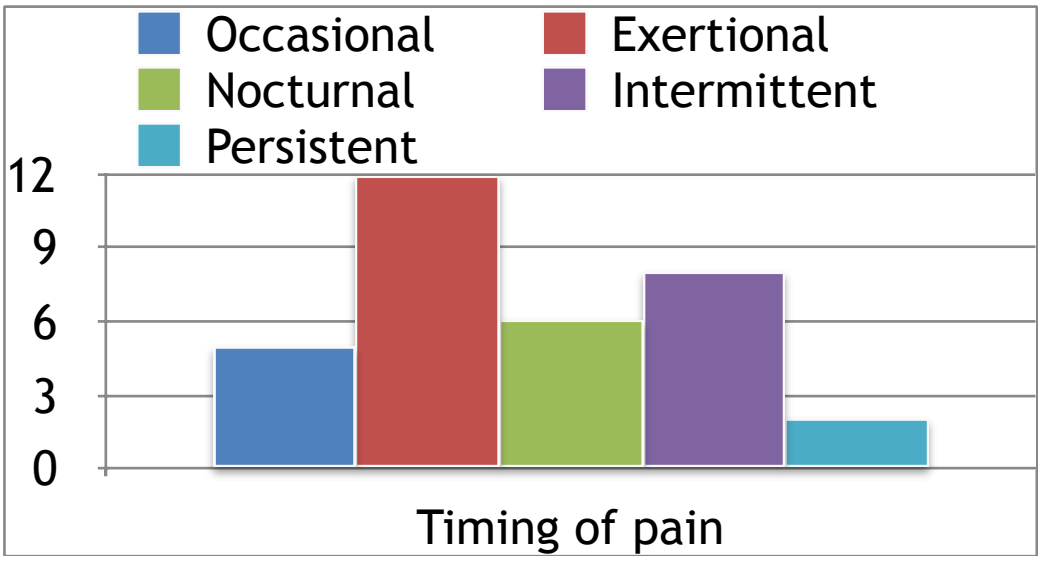
with 19 patients complaining of it. 8 patients complained of dull aching pain. 4 patients complained of burning type of pain and 2 complained of a sharp pain.



The severity of the pain experienced by the patients was determined using the Visual Analog Scale. The severity ranged from VAS scores of 2 to 10. The sample was arbitrarily divided



into mild, moderate or severe pain based on cut-off VAS scores of 5 and 8. Mild pain was seen in 4 patients, moderate pain in 21 patients and severe pain in 8 patients.

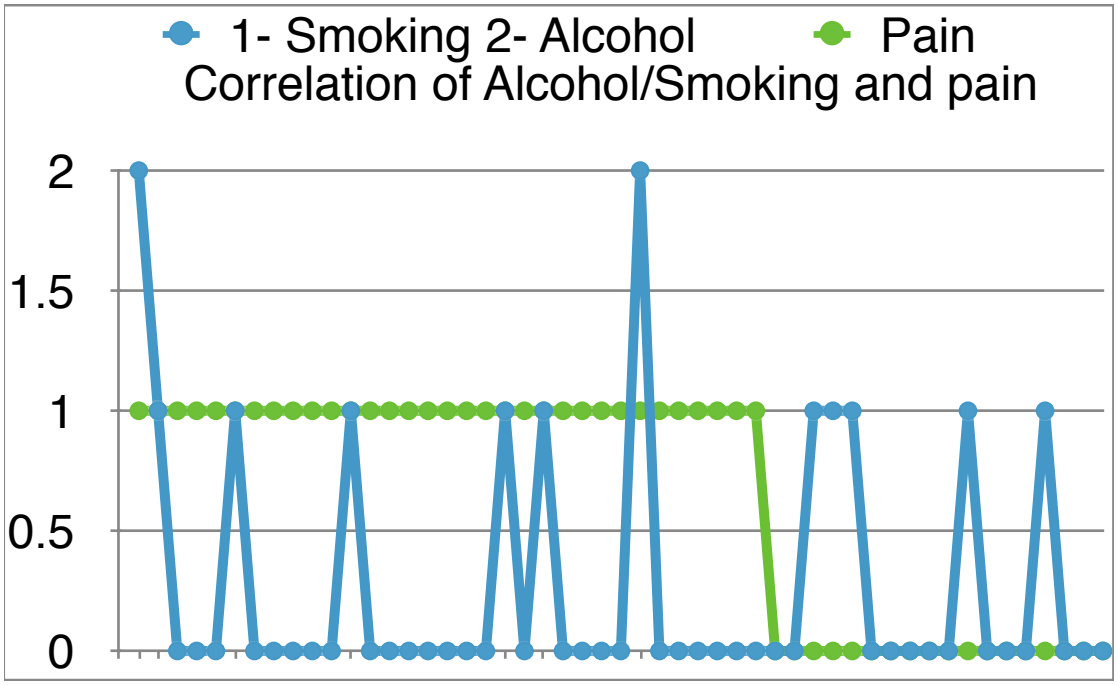


The timing of the pain was varied among the sample studied. Most commonly the pain was exertional, seen in 12 patients, intermittent in 8 patients, nocturnal pain was seen in 6 patients, pain was occasional in 6 patients and pain remained persistent in only 2 patients.

Among the patients complaining of pain, 20 had an improvement in pain on antiparkinsonian drug intake while 13 had no response. No patients complained of a worsening of pain on drug intake.

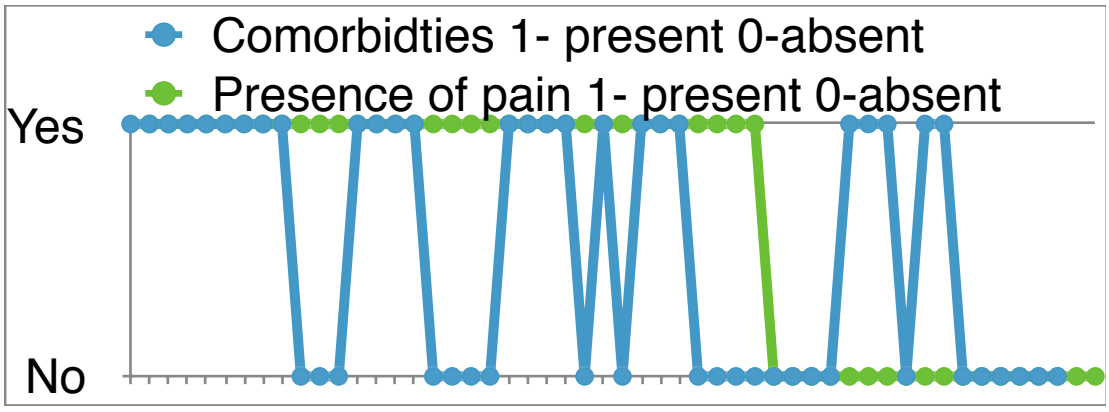
Of the 51 patients in the sample, 38 did not consume alcohol or smoke tobacco. Of those who reported pain, 4 consumed alcohol while 2 were smokers. Of those without pain 4 consumed alcohol and 3 were tobacco smokers.

The correlation between the use of tobacco products and/or alcohol and the presence of pain was calculated. The value of R is -0.0046. Although there is a negative correlation, the relationship between the variables is weak and hence not a significant finding.



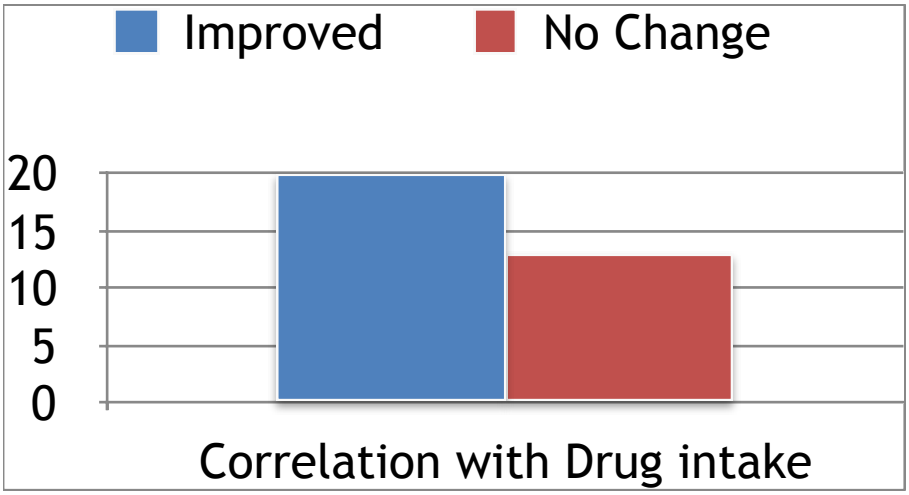
In the sample studied, comorbidities were seen in 37 of the 51 patients. In 32 patients it was not associated with pain, while in the remaining 5 there was presence of pain.

The correlation between the presence of comorbidities and the presence of pain was calculated. The value of R is 0.3428. Although there is a positive correlation, the relationship



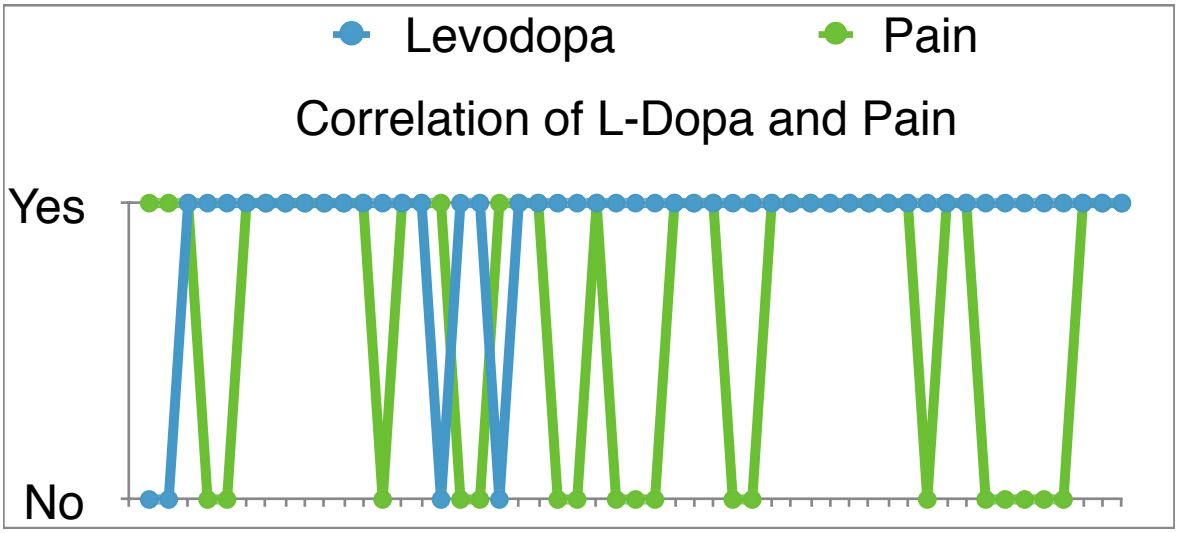
between the variables is weak and hence not a significant finding.

Of the sample studied with the presence of pain, levodopa was taken in all of them. 16 had decrease in pain with drug intake while 11 had no change. Among those taking anticholinergics, 12 had decrease in pain and 8 had no change. In those on dopa



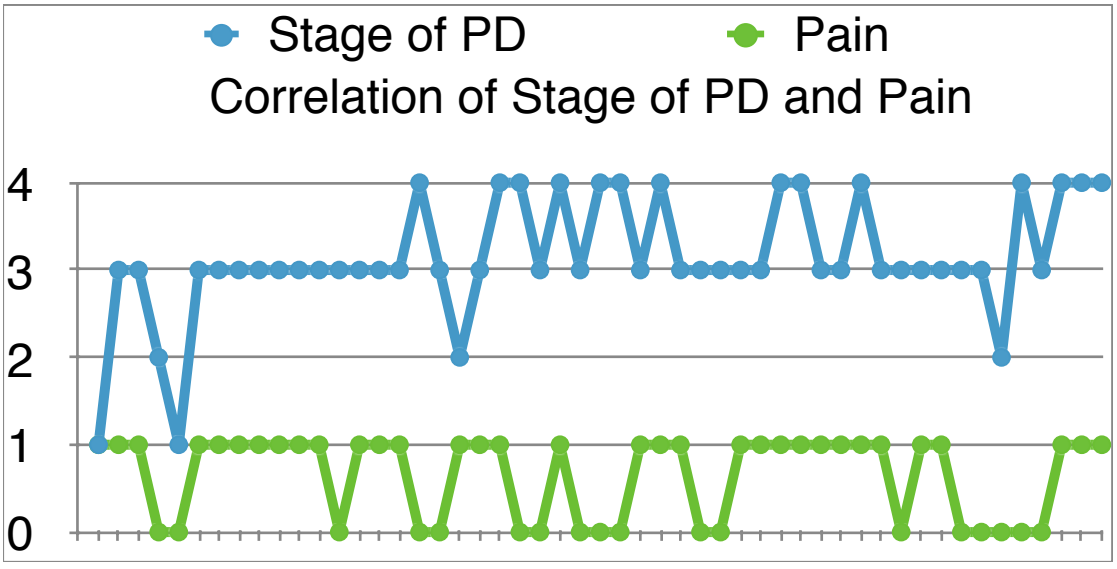
agonists, pain decreased in 8 and there was no change in 2. However there were no patients without pain who were taking dopa agonists. No pain-free individuals were on single- drug regimen. The correlation between the use of levodopa , anticholinergics and dopa agonists and the presence of pain was calculated. The R value for levodopa was -0.2155. For anticholinergics, R value was -0.2966. Dopa agonist had R value of 0.2437. The relationship between the variables is weak and hence not a significant finding.

There is a poor positive correlation of R=0.0382 between duration of disease and the presence of pain. This is not



statistically significant.

The correlation between the stage of Parkinson's Disease and presence of pain was calculated. The R value is 0.0879 which

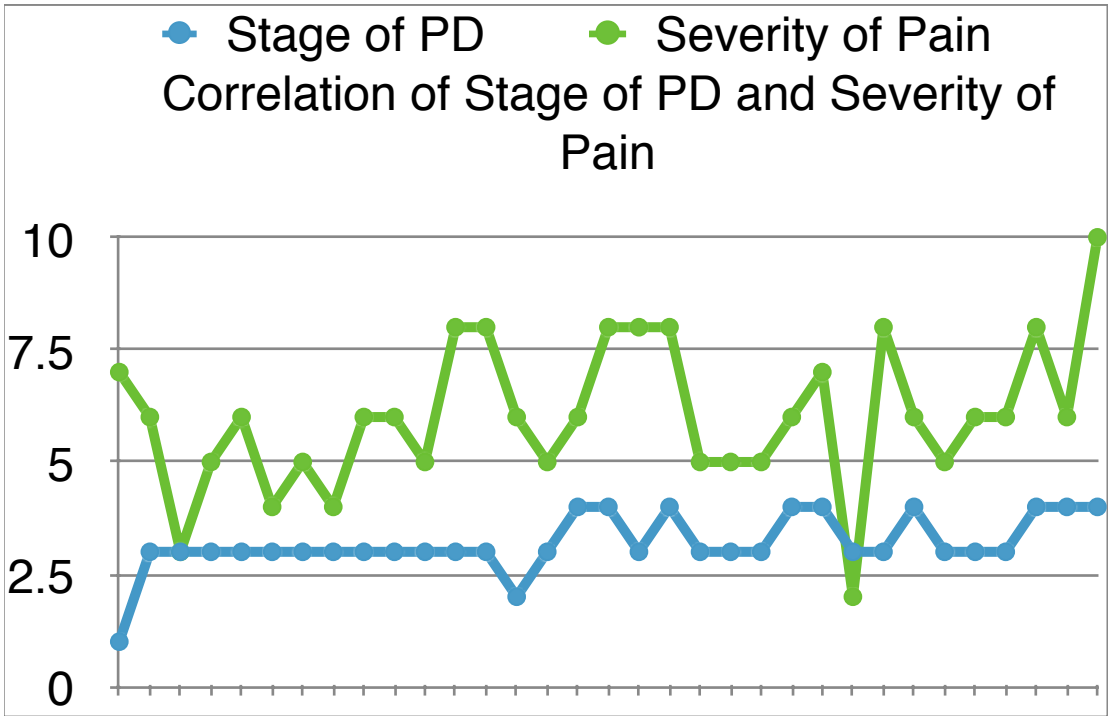


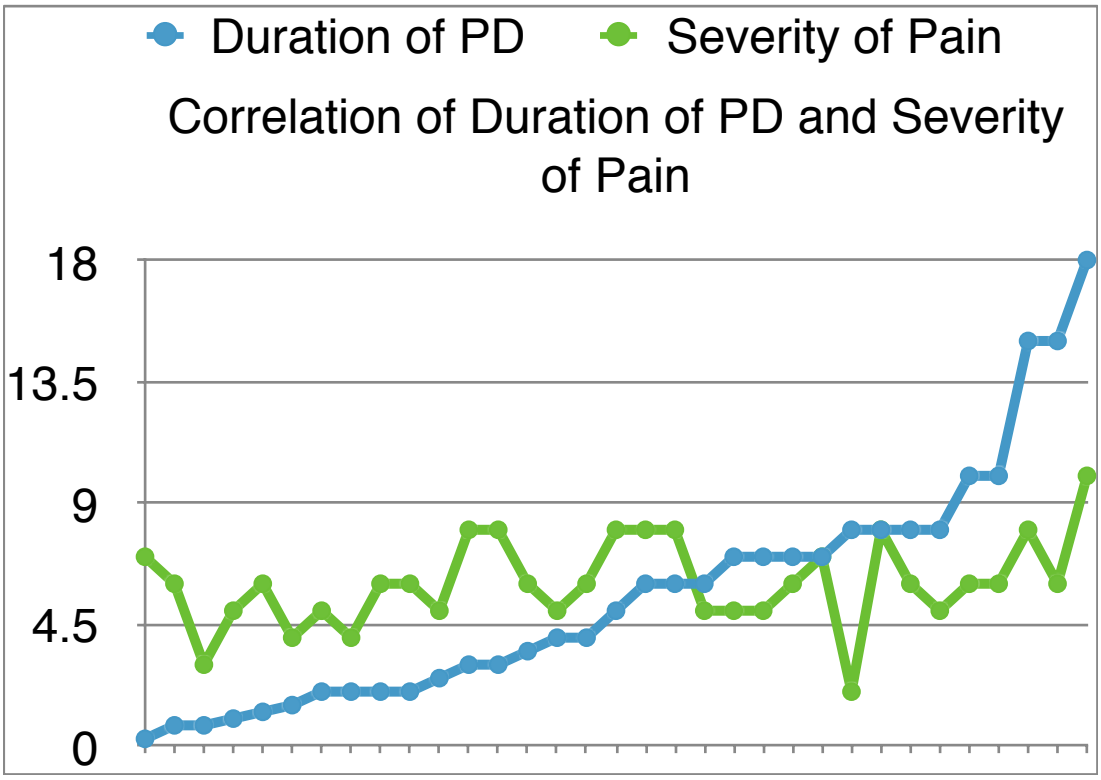
showed a weak correlation and is not statistically significant.

The correlation between the presence of comorbidities and severity of pain was calculated. The R value is -0.0247. The R value for correlation between smoking or alcohol and severity of pain was -0.0191. This was a negative correlation, but not statistically significant.

The correlation between the duration of disease and the severity of pain was statistically insignificant with a R value of 0.3749. This was a weak positive relationship.

The staging of disease also did not have a significant correlation with severity of disease. The R value was 0.2632, which was a weak positive correlation.





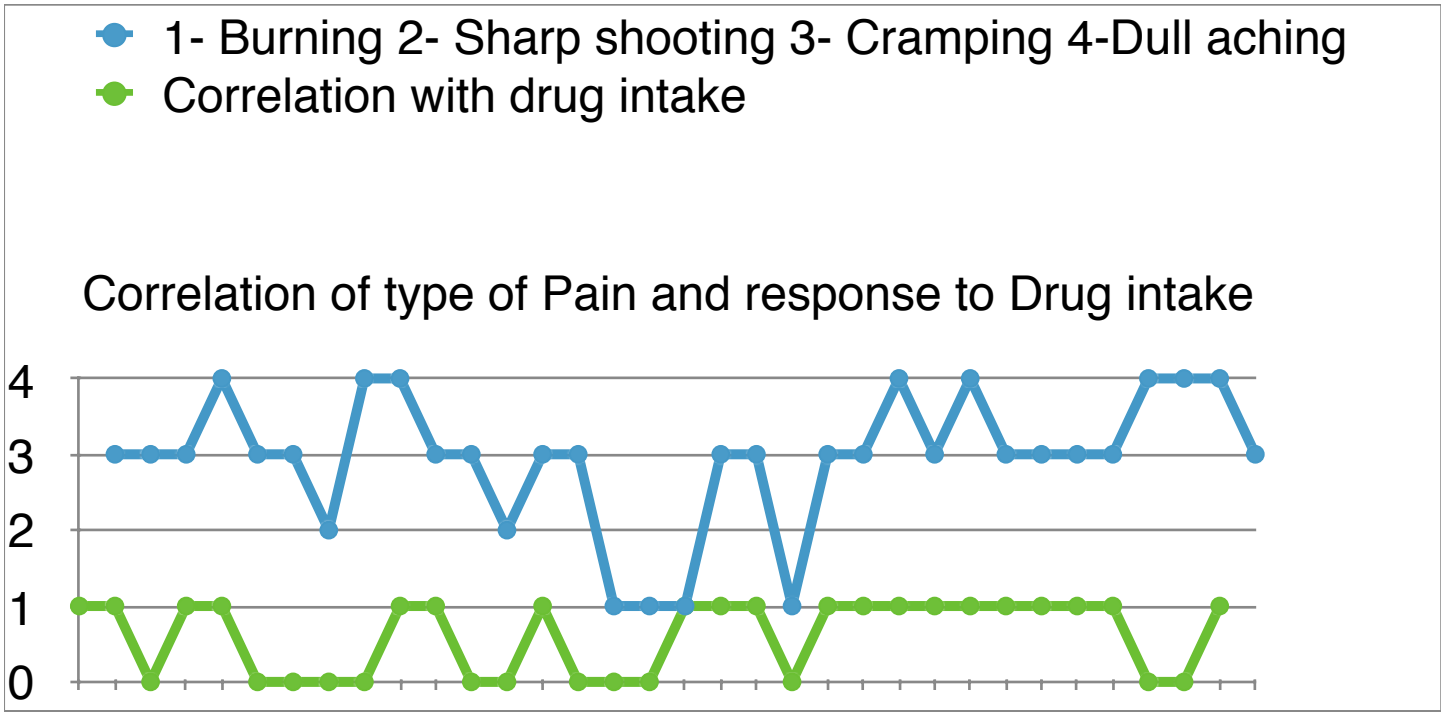
The correlation of severity of pain and use of levodopa was not significant with R value of -0.1646. This showed a weak negative correlation.

The stage of the of the disease does not have any significant effect on the pain experienced by the patient. It was found to be statistically insignificant. (p=0.499)

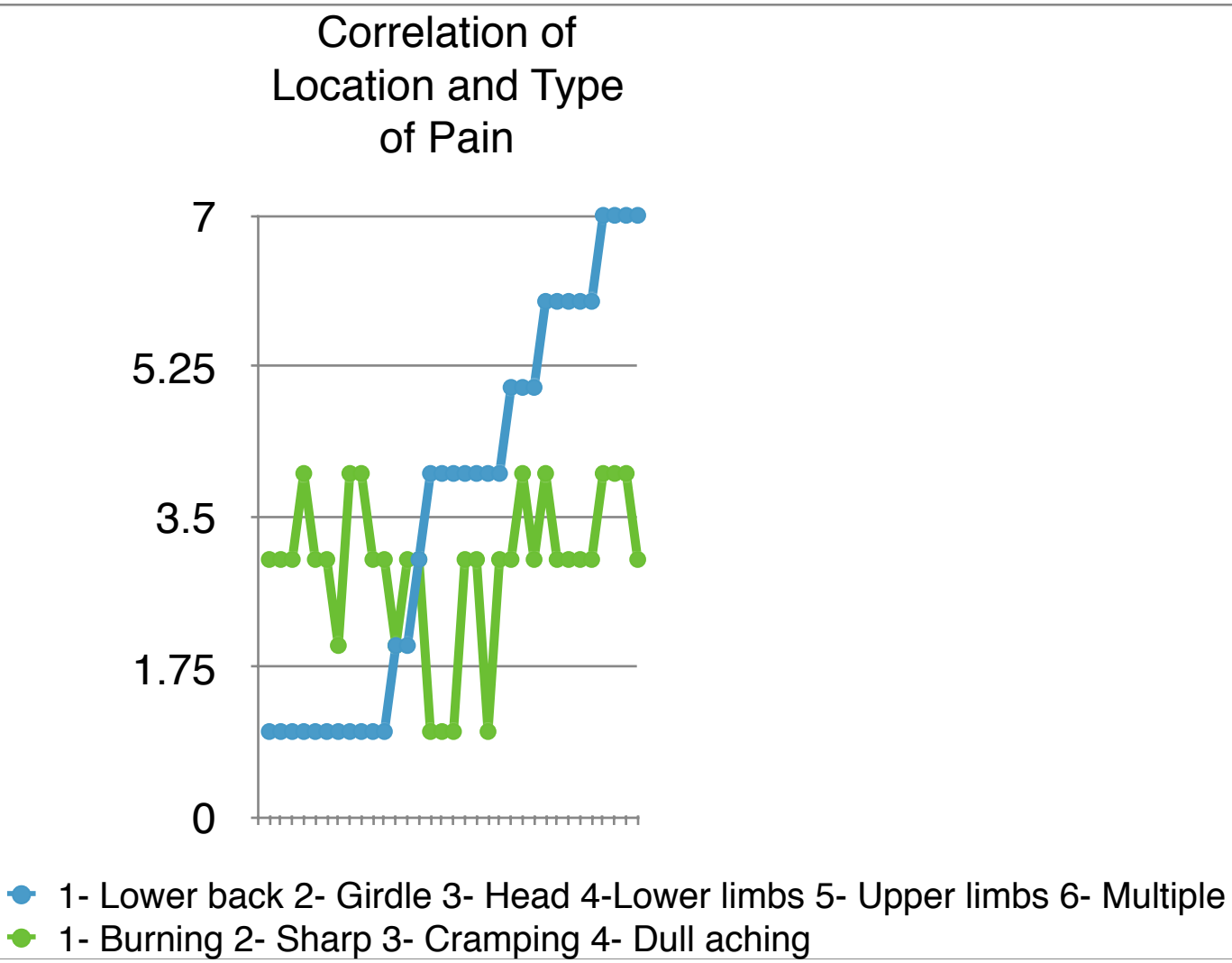
The stage of the disease does not have any significant effect on the severity of pain experienced by the patient. The effect of the stage of disease on severity of pain was statistically insignificant. (p=0.499)

The duration of disease does not have a significant effect on the severity of pain experienced by the patient. The effect was statistically insignificant.(p=0.3424)

There was no significant effect of the drug intake on pain based on the type of pain experienced. (p=0.4295)



There was no significant effect of the type of pain on the location of pain experienced by the patient. (p=0.4648)



The type of pain experienced did not have a significant effect on the severity of the pain experienced. p=0.4819

DISCUSSION

The study was done on a small sample of 51 patients. The study showed a prevalence of pain of 68.62%. This was similar to previous studies which had demonstrated a prevalence of 40-80%. The prevalence in women was 87.5% and in men was 54.28%. This was in keeping with previous studies which has postulated female sex as a risk factor for pain. However the correlation between the sex of the patient and the presence of pain was statistically significant.

The most common location of the pain was the lower back, which was

in contrast to pre-existing studies which had reported lower limb pain as the most common.

Most of the patients complained of a moderate severity of pain with very few complaining of high severity.

The moat common type of pain was cramping, musculoskeletal pain. This was again the same as reported in previous studies. The musculoskeletal pain was most common in the lower back. Central type of pain was seen most commonly in the lower limbs. Radicular pain was reported only in the lower back. Akathisia and dystonic pain was not reported by any of the patients.

The most common timing of the pain was on exertion. Persistent pain was very rarely seen. Patients reported an improvement in the pain on anti-parkinsonian drug intake. It was seen in 60.6% of pain while the rest of the patients had no change on drug intake. No patients complain of a worsening of pain on drug intake. This correlates with the finding that there was no reported dystonic pain.

The study showed a weak positive correlation between the presence of comorbidities and the presence of pain. This needs to be validated using a larger sample size.

The use of levodopa had a weak negative correlation with the presence of pain, without statistical significance. This was similar to previous studies which showed a decreased prevalence of spontaneous pain on levodopa use.

A similar effect was seen with anticholinergic use. However dopamine agonist had a weak positive correlation to presence of pain. This suggests a possible different mechanism of action for levodopa for decreasing pain.

The duration of the Parkinson's Disease showed a weak positive correlation with the severity of pain experienced. This suggests that pain can be part of the natural history of the history with the spread of the disease pathology to areas of pain processing.

This is also reflected in the weak positive correlation between the stage of the disease with the severity of pain.

Use of levodopa has a negative correlation with the severity of pain but it was not statistically significant. This probably reflects the small size of the sample in the study and needs more work to be clinically validated.

Conversely, use of dopa agonists was associated with a higher severity of pain. However the correlation was weak and not statistically significant.

In patients with pain, the use of dopa agonists showed a more frequent improvement in pain on drug intake. However the correlation is not statistically significant.

Taking both these findings into consideration, there is a possibility that dopamine agonist use has better effect on control of pain than other drugs. However this needs to be validated in further studies.

The type of pain correlated better with response to drugs. This is probably due to the effect of drugs on rigidity and stiffness, which can improve the musculoskeletal pain in these patients.

LIMITATIONS OF THE STUDY:

1. The size of the sample is small

2. The data collection was from a single centre
3. The classification and severity of pain were both subjective and highly arbitrary
4. No objective measures were used

CONCLUSION

In Parkinson's Disease, the presence of pain is much more common than is widely known. The pain is more common in the female population and is most commonly of the musculocutaneous type with moderate severity and located in the lower back.

The presence of pain seems to depend on other comorbidities and absence of alcohol or smoking. Dopamine agonist seems to be associated with a higher prevalence as well as severity of pain. This seems to point to a possible causal relationship.

The presence of pain did not correlate with the duration and severity of pain however the severity of pain was. This suggests that the progression of disease increases the pain only in those in whom it is already present.

This study did not look at the effect of pain on the quality of life in patients with Parkinson's Disease.

The effect of drugs on pain threshold could not be reliably tested due to the absence of objective testing in the study. There is evidence that drug intake primarily improves the musculoskeletal pain rather than other types of pain.

This study was limited by the size of the sample. The absence of an objective testing of pain threshold also limited the scope of the study. Further studies with larger sample sizes and use of

objective testing systems along with detailed scoring scales to collect more data regarding related data such as non-motor complications of pain, are needed.

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ANNEXURES

ABBREVIATIONS

PD	- Parkinson's Disease
VAS	- Visual Analog Scale
SSR	- Sympathetic Skin Response
LEP	- Laser Evoked Brain Potentials
NFR	- Nociceptive Flexion Response
PET	- Positron Emission Tomography
MRI	- Magnetic Resonance Imaging
UKPDS	- United Kingdom Parkinson's Disease Society
MDS	- Movement Disorder Society
HY	- Hoehn and Yahr Staging system

PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

IP/OP NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

CARE GIVER :

PAST HISTORY : Diabetes mellitus:

Systemic hypertension:

Chronic Kidney Disease

Others:

TREATMENT HISTORY:

CLASS OF DRUG	WHETHER TAKEN
Levodopa	
Anticholinergics	
Dopamine agonist	
MAO-B inhibitors	

PERSONAL HISTORY : Smoking :

Alcohol:

Other substance abuse:

DURATION OF PARKINSON'S DISEASE:

STAGING OF PARKINSON'S DISEASE:

Hoehn & Yahr stage
0: No visible symptoms of Parkinson's disease
1: Parkinson's disease symptoms just on one side of the body
2: Parkinson's disease symptoms on both sides of the body and no difficulty walking
3: Parkinson's disease symptoms on both sides of the body and minimal difficulty walking
4: Parkinson's disease symptoms on both sides of the body and moderate difficulty walking
5: Parkinson's disease symptoms on both sides of the body and unable to walk

PRESENCE OF PAIN :

LOCATION OF PAIN : Head and neck

Upper limbs- Proximal

Distal

Lower Limbs- Proximal

Distal

Trunk- Chest

Abdomen

Groin

Back- Upper

Lower

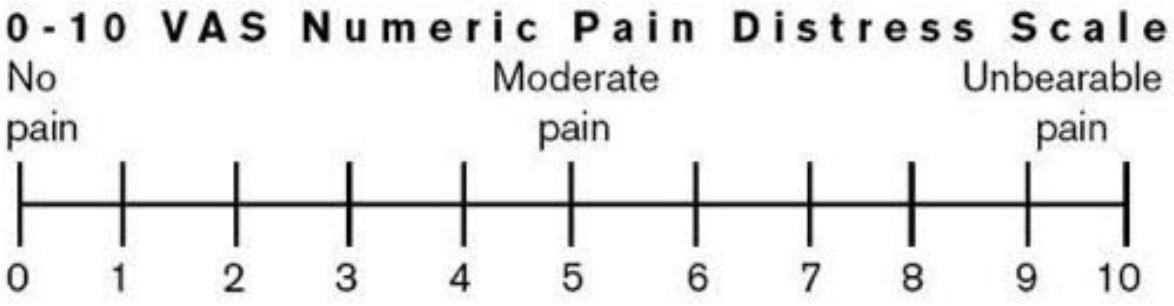
TYPE OF PAIN : Sharp/Shooting

Dull aching

Burnished

Cramping

SEVERITY OF PAIN:



TIMING OF PAIN: Persistent

Intermittent

Occasional

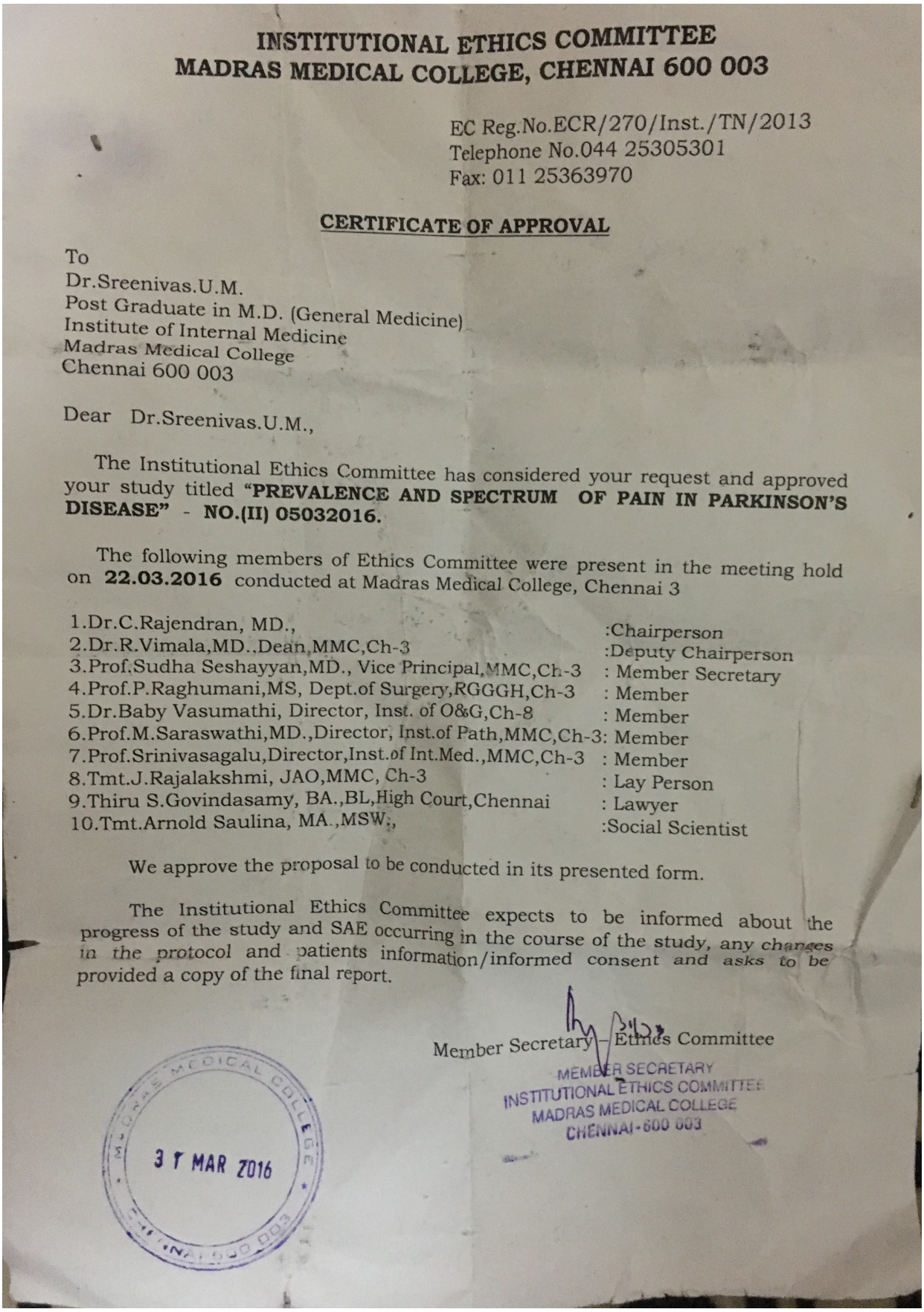
Diurnal variation

CORRELATION WITH DRUG INTAKE: Increased

Decreased

No change

CERTIFICATE OF APPROVAL



INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Sreenivas.U.M.
Post Graduate in M.D. (General Medicine)
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.Sreenivas.U.M.,

The Institutional Ethics Committee has considered your request and approved your study titled **"PREVALENCE AND SPECTRUM OF PAIN IN PARKINSON'S DISEASE" - NO.(II) 05032016.**

The following members of Ethics Committee were present in the meeting hold on **22.03.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
5.Dr.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
6.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
7.Prof.Srinivasagalu,Director,Inst.of Int.Med.,MMC,Ch-3	: Member
8.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

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

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

MADRAS MEDICAL COLLEGE
31 MAR 2016
CHENNAI-600 003

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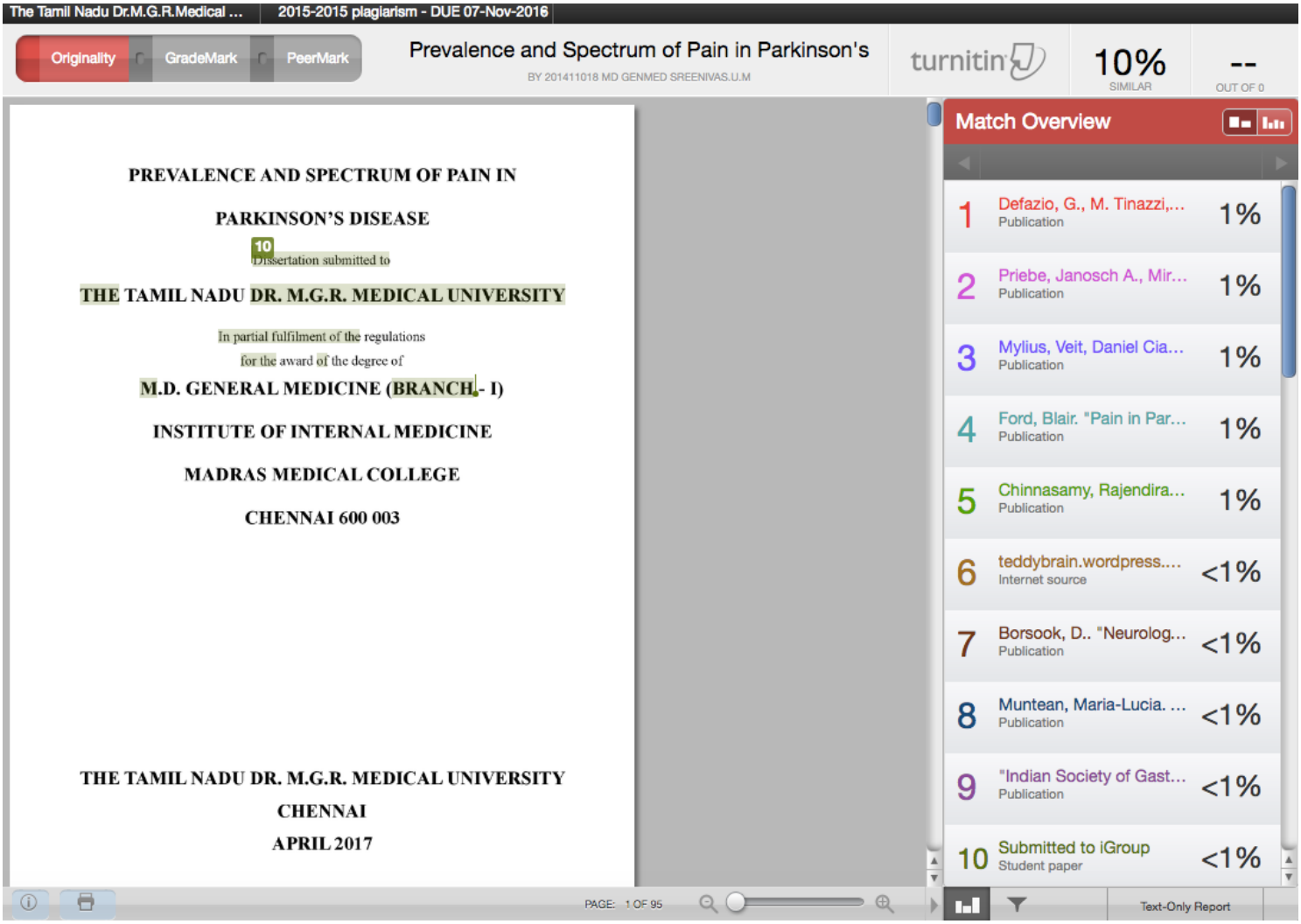

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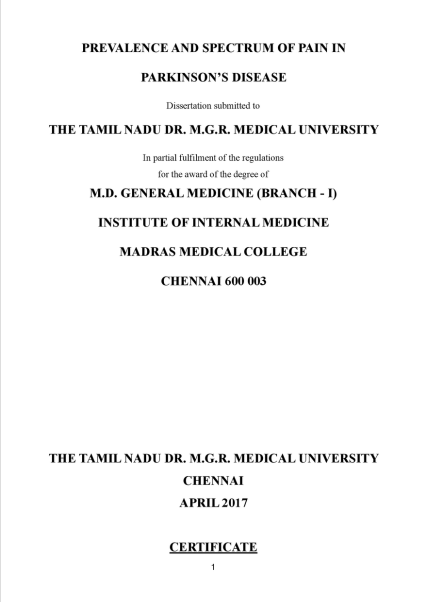

PREVALENCE AND SPECTRUM OF PAIN IN

PARKINSON'S DISEASE

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfilment of the regulations
for the award of the degree of

M.D. GENERAL MEDICINE (BRANCH - I)

INSTITUTE OF INTERNAL MEDICINE

MADRAS MEDICAL COLLEGE

CHENNAI 600 003

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI
APRIL 2017

CERTIFICATE
1

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜிவ் காந்தி அரசு பொது மருத்துவமனையில் பார்க்கின்சன்'ஸ் நோய் பற்றிய ஒரு ஆராய்ச்சி நடைபெற்று வருகிறது.

பார்க்கின்சன்'ஸ் நோயினால் பாதிக்கப்பட்ட நபர்களின் உடல் வலி பற்றி அறிவதே இந்த ஆராய்ச்சியின் நோக்கமாகும்.

நீங்கள் இந்த ஆய்விற்கு தகுதியானவர்களாக இருக்கும் பட்சத்தில் தங்களின் மருத்துவ விவரத்தையும், ஆய்வக பரிசோதனை அறிக்கையும் ஆய்வு நோக்கங்களுக்காக பயன்படுத்தபடும்.

இந்த ஆய்வில் பங்குபெற வேண்டுமா வேண்டாமா என்பதை நீங்களே தீர்மானித்துக் கொள்ளலாம். நீங்கள் இந்த ஆய்வில் பங்குபெற மறுக்கவோ, விலகிக்கொள்ளவோ, நீங்கள் தந்த ஆய்வுக்குறிப்புகளை அழிக்கவோ எந்த நேரத்திலும் எந்தவித நிபந்தனையும் இன்றி செயல்படுத்த உங்களுக்கு உரிமை உள்ளது.

இந்த ஆய்வில் பங்கு பெறுவதால் உங்களுக்கு எந்த ஆபத்தும் வராது என்பதை உறுதி செய்கிறோம். தன்னார்வத்துடன் கலந்துகொள்ளும் இந்த ஆய்விற்கு எந்த ஊதியமும் கிடையாது.

நீங்கள் விரும்பினால் இந்த ஆராய்ச்சியின் மூலம் கண்டறிந்தவற்றை உங்களுடன் பகிர்ந்து கொள்ள எந்த தடையும் இல்லை.

அந்தரங்கம்:

இந்த ஆய்வின் பொழுது சேகரிக்கப்பட்ட குறிப்புகள் அனைத்தும் ரகசியமாக வைக்கப்படும்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

INFORMATION SHEET

We are conducting a study on "PREVALENCE AND SPECTRUM OF PAIN IN PARKINSON'S DISEASE" among patients attending Rajiv Gandhi Government General Hospital, Chennai

The purpose of this study is to assess "PREVALENCE AND SPECTRUM OF PAIN IN PARKINSON'S DISEASE"

We are selecting certain cases and if you are found eligible, we may be using clinical profile, lab test reports and radiological reports for study purposes which does not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator
Date:
Place:

Signature of Participant / Guardian

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு: **பார்க்கின்சன்'ஸ் நோயினால் பாதிக்கப்பட்ட நபர்களின் உடல் வலி பற்றிய**

ஆராய்ச்சி

ஆய்வு நிலையம்: பொது நல மருத்துவத்துறை
சென்னை மருத்துவக் கல்லூரி
சென்னை - 600003

பெயர்: தேதி: வயது: பால்:

ஆய்வு விவரங்களை எனது சொந்த மொழியில் எனக்கு விளக்கினார். எனக்கு சந்தேகம் கேட்க ஒரு வாய்ப்பும், அதற்கு தகுந்த பதில்களும் வழங்கப்பட்டது.	❑
நான் இந்த ஆய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்திலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	❑
இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்பதற்க்கு என் அனுமதி தேவை இல்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்	❑
இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்கள்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் நான் முழு மனதுடன் ஒப்புக்கொள்கிறேன்	❑
நான் ஆய்வில் பங்கேற்க ஒப்புக்கொள்கிறேன். நான் மருத்துவரிடம் உண்மையாக இருப்பேன் என உறுதியளிகிறேன்	❑

ஆய்வாளரின் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

ஆய்வாளரின் பெயர்: டாக்டர். **உ.மி. சீனிவாஸ்** பங்கேற்பாளர் பெயர் / முகவரி

PATIENT CONSENT FORM

Study Detail	:	PREVALENCE AND SPECTRUM OF PAIN IN PARKINSON'S DISEASE
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination , biochemical and radiological tests ❑

Signature of Investigator
Study Investigator's Name:

Signature/thumb impression
Patient's Name and Address:

MASTER CHART

	Age	SEX	Co-morbidities	Personal History	Duration of PD	Staging of PD	L-Dopa	Anticholinergics	Dopa Agonist	MAO-B inhibitors	Presence of Pain	Location	Type	Severity - VAS	Timing	Correlation with drug intake
1																
2	62	Female	DM-10yrs, SHT- 10yrs		18	Stage 4	☑	☐	☑	☑	Yes	Back- Lower	Cramping	10	Intermitttent	Decreased
3	50	Male		Alcohol- 20 years stopped	3	Stage 3	☑	☑	☐	☐	Yes	Limbs- lower	Burning	8	Nocturnal	Decreased
4	68	Female	Dm-6 yr, Hypothyroid		6	Stage 4	☑	☑	☐	☑	Yes	Limbs- lower	Burning	8	Nocturnal	No change
5	60	Male			6	Stage 3	☑	☑	☐	☐	Yes	Back- Lower	Cramping	8	Exertional	Decreased
6	60	Male			8	Stage 3	☑	☑	☐	☐	Yes	Limbs- lower	Cramping	8	Nocturnal	No change
7	60	Female	SHT- 2yrs		5	Stage 4	☑	☑	☐	☐	Yes	Back- Lower	Cramping	8	Exertional	No change
8	61	Male	DM-4 yr, SHT-4yr, Dyslipidemia -4yrs	Alcohol- stopped 6 yrs back	3	Stage 3	☐	☑	☑	☐	Yes	Limbs- upper	Cramping	8	Intermitttent	Decreased
9	75	Female	Sht-15 yrs, dyslipidemia		15	Stage 4	☑	☑	☐	☐	Yes	Limbs- upper	Cramping	8	Occasional	Decreased
10	54	Female			0.25	Stage 1	☐	☐	☑	☑	Yes	Multiple	Cramping	7	Exertional	Decreased
11	56	Male	Sht- 6 months		7	Stage 4	☑	☑	☑	☐	Yes	Multiple	Cramping	7	Persistent	Decreased
12	47	Female			15	Stage 4	☑	☑	☐	☐	Yes	Multiple	Cramping	6	Intermitttent	Decreased
13	61	Male			7	Stage 4	☑	☑	☑	☑	Yes	Limbs- lower	Cramping	6	Intermitttent	Decreased
14	66	Male	DM, SHT-15 yrs	Smoking- occasional	8	Stage 4	☑	☐	☑	☐	Yes	Multiple	Cramping	6	Intermitttent	Decreased
15	72	Female	SHT-5yrs		4	Stage 4	☑	☑	☐	☐	Yes	Back- Lower	Cramping	6	Exertional	Decreased
16	75	Female			2	Stage 3	☑	☑	☐	☐	Yes	Neck and shoulders	Cramping	6	Occasional	Decreased
17	81	Male	SHT	Smoking- stopped 20 yrs	0.75	Stage 3	☐	☐	☐	☐	Yes	Back- Lower	Cramping	6	Exertional	No change
18	67	Female	Hypothyroid		10	Stage 3	☑	☐	☑	☑	Yes	Back- Lower	Dull aching	6	Exertional	Decreased
19	72	Female	CAD		2	Stage 3	☑	☐	☐	☐	Yes	Neck and shoulders	Dull aching	6	Intermitttent	Decreased

	Age	SEX	Co-morbidities	Personal History	Duration of PD	Staging of PD	L-Dopa	Anticholinergics	Dopa Agonist	MAO-B inhibitors	Presence of Pain	Location	Type	Severity - VAS	Timing	Correlation with drug intake
37	52	Male			2	Stage 3	✓	✓			No			0		
38	53	Male	DM-4yrs	Smoking alcohol - stopped 10 yrs	3	Stage 3	✓	✓			No			0		
39	55	Male			5	Stage 4	✓	✓			No			0		
40	58	Male			4	Stage 3	✓	✓			No			0		
41	61	Male			0.75	Stage 1	✓	✓			No			0		
42	62	Male			10	Stage 3	✓	✓			No			0		
43	64	Female	Dyslipidemia -10 yrs		0.75	Stage 2	✓			✓	No			0		
44	65	Male	DM- 7 yrs		5	Stage 4	✓	✓			No			0		
45	66	Male			5	Stage 3	✓	✓			No			0		
46	67	Male		Smoker, alcohol- stopped 7 yrs	6	Stage 3	✓	✓			No			0		
47	67	Male		Alcohol stopped 5 yrs	10	Stage 2	✓	✓			No			0		
48	67	Male			6	Stage 3	✓	✓			No			0		
49	68	Male		Alcohol- stopped 5 yrs	4	Stage 4	✓	✓			No			0		
50	72	Male		Snuff- stopped 5 yrs	11	Stage 4	✓	✓			No			0		
51	75	Female	SHT-15 yrs		13	Stage 3	✓			✓	No			0		
52	76	Male			3	Stage 4	✓	✓			No			0		

1	Age	SEX	Co-morbidities	Personal History	Duration of PD	Staging of PD	L-Dopa	Anticholinergics	Dopa Agonist	MAO-B inhibitors	Presence of Pain	Location	Type	Severity - VAS	Timing	Correlation with drug intake
20	74	Male	Dm- 6mth, SHT- 3 yr		1.25	Stage 3	☑	☐	☐	☐	Yes	Neck and shoulders	Dull aching	6	Occasional	No change
21	77	Male	CAD 10 yrs		10	Stage 3	☑	☐	☑	☑	Yes	Multiple	Dull aching	6	Intermitttent	Decreased
22	66	Male	CAD, Dyslipidemia		3.5	Stage 2	☐	☐	☑	☑	Yes	Back- Lower	Sharp/ shooting	6	Exertional	No change
23	75	Male	GERD		7	Stage 3	☑	☑	☐	☐	Yes	Limbs- lower	Burning	5	Exertional	No change
24	50	Female			1	Stage 3	☑	☑	☐	☐	Yes	Girdle	Cramping	5	Exertional	No change
25	57	Male	SHT-15yrs, CKD-1yr	Smoker- stopped 18 yrs, Alcohol- regular,stopped 1.5yr	4	Stage 3	☑	☑	☐	☐	Yes	Back- Lower	Cramping	5	Nocturnal	Decreased
26	61	Male		Alcohol occasional	2	Stage 3	☑	☑	☐	☐	Yes	Back- Lower	Cramping	5	Exertional	Decreased
27	66	Female			6	Stage 3	☑	☑	☐	☐	Yes	Limbs- lower	Cramping	5	Nocturnal	Decreased
28	76	Female	SHT- 10 yrs, Hypothyroid- 6 yrs		2.5	Stage 3	☑	☐	☐	☑	Yes	Head	Cramping	5	Intermitttent	Decreased
29	68	Male			8	Stage 3	☑	☑	☐	☐	Yes	Neck and shoulders	Dull aching	5	Persistent	No change
30	69	Male	Hypothyroid		7	Stage 3	☑	☐	☑	☑	Yes	Back- Lower	Dull aching	5	Exertional	No change
31	75	Male	SHT- 15 yrs, CAD		2	Stage 3	☑	☐	☐	☑	Yes	Back- Lower	Dull aching	4	Exertional	No change
32	48	Male		Alcohol stopped 1 yr	1.5	Stage 3	☑	☑	☐	☐	Yes	Girdle	Sharp/ shooting	4	Occasional	No change
33	80	Male	SHT- 20 yrs		0.75	Stage 3	☑	☐	☐	☑	Yes	Limbs- upper	Dull aching	3	Occasional	Decreased
34	69	Female	DM-15 yrs		8	Stage 3	☑	☑	☐	☐	Yes	Limbs- lower	Burning	2	Nocturnal	No change
35	43	Male	SHT-10yrs		10	Stage 3	☑	☑	☐	☐	No			0		
36	51	Male			8	Stage 3	☑	☑	☐	☐	No			0		