كليـــــــة الـطـب
والصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH

MARRAKECH
جامعة القاضي عياض
UNIVERSITÉ CADI AYYAD

Year 2019 Thesis N° 199

Neuropsychiatric manifestations in idiopathic Parkinson's disease

THESIS

PRESENTED AND DEFENDED PUBLICLY ON 11/07/2019

BY

Mr. Raymond KLEVOR

Born on 07 January 1991 in Ghana

TO OBTAIN A MEDICAL DOCTORATE

KEYWORDS

Parkinson's Disease – Neuropsychiatric Manifestations – Fluctuations
L-Dopa – Quality of Life

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Mr.	H. GHANNANE Professor of Neurosurgery	

HIPPOCRATIC OATH

***A*t the time of being admitted as a member of the medical profession:**

***i* solemnly** pledge to dedicate my life to the service of humanity;

the health and well-being of my patient will be my first consideration;

***i* will** respect the autonomy and dignity of my patient;

***i* will** maintain the utmost respect for human life;

***i* will** not permit considerations of age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between my duty and my patient;

***i* will** respect the secrets that are confided in me, even after the patient has died;

***i* will** practice my profession with conscience and dignity and in accordance with good medical practice;

***i* will** foster the honour and noble traditions of the medical profession;

***i* will** give to my teachers, colleagues, and students the respect and gratitude that is their due;

***i* will** share my medical knowledge for the benefit of the patient and the advancement of healthcare;

***i* will** attend to my own health, well-being, and abilities in order to provide care of the highest standard;

***i* will** not use my medical knowledge to violate human rights and civil liberties, even under threat;

***i* make these promises solemnly, freely and upon my honour.**

Declaration of Geneva, 1948

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LISTE ARRÉTÉÉ LE 22/04/2019

DEDICATION

*To my **parents** who believe in me*

*To an older **brother** who found me*

*To a younger **sister** who longs to see me*

*And, to the many **few** whom stance and circumstance*

Have brought my way.

Our paths have crossed per fate or per chance;

It's the same anyway

Because my life without you – I can't imagine!

So, thank you for the eyes that have gazed

And, not only gazed,

For we have shed many a tear together

And, we have shared our hearts together.

Still, I can't imagine.

So, thank you for the ears that listened

To the heart broken, and the soul weakened.

Thank you for the hands that were strong

And the words that became a song

From the burning flames of your hearts.

Thank you from the depths of my heart.

ACKNOWLEDGEMENTS

Pr. Fatima ASRI

The glow of your person – that is what touched our hearts as your students. It was a beautiful experience to have had the opportunity to interne in your department. A short experience with lasting memories. I am very grateful that you agreed to preside over the jury. I feel lucky. It is an honor, professor.

Thank you.

"Here comes the sun." *From Abbey Road by George Harisson*

Pr. Mohamed CHRAA

This here can't be enough. Maybe words indeed aren't enough. Because from the moment I approached you for my thesis you have been more than I could ever imagine. You are exceptional. But again, words aren't enough. You are the person we want to be but might never come close to being because if we get to be half the person you are, it would be one great achievement of a lifetime. But alas, words! If only I had enough of them!

Thank you, sir.

"But truly, if I were not Alexander, I wish I were Diogenes." *Alexander by Plutarch*

Pr. Fatiha MANOUDI

I can remember a role-playing session we had with you where we had to bring to life a case of a young man in the throes of addiction. It is this vivid picture that comes to mind each time we hear your name. It is that liveliness that you infuse into us, that theatrical passion – the art, performance that has left us with one certainty: we will make better doctors because of you. It is an honor, professor.

Thank you.

"O body swayed to music, O brightening glance/ How can we know the dancer from the dance?" *Among School Children by W. B. Yeates*

Pr. Houssine El GHANNANE

Thank you sir! We will always remember you fondly because of the way you treat us – calmly, understandingly with that paternal touch. Yes, the paternal touch. I remember when I came to petition your acceptance to be on the panel – I really can't forget this – you kept saying yes, yes, yes…before I even landed. You knew what I was after before I made it known, and you accepted before I even asked. We are lucky to have you as our teacher.

Thank you.

"A learner with the simplest, a teacher of the thoughtfullest…" *Song of Myself by Whitman*

Pr. Nisrine LOUHAB

How could I forget you, professor? I can still remember in my neurology rotation, fourth year, I think, having to give a presentation on the Cerebellar syndrome. And, from that day, I understood that simple things make the difference because you were simply ready to give your best to us. You have touched many lives than you might know, and indeed, professor, I am one better because of you.

Thank you.

"One by one they came/ As far as the eye could see/ Each one somehow touched By your generosity." *Thank You by Ray Boltz*

Pr. Najib KISSANI

You yearn for knowledge. It is that verve with which you seek to know that also pushes you to demand the best of us. You want us to be the best of ourselves. You want us to challenge ourselves. You want us to go far in our lives.

Thank you, sir.

"Someone will remember us, I say, even in another time." *A translated line from Sappho's Fragments.*

The Neurology and Neurosurgery teams

You might not know it but you are remembered with admiration. You are an inspiration. You guys break your backs to mend others. May your training be filled with joy, and may you succeed in all your endeavors. Drs. Traoré, Jalami, Asmae, Khadija… Drs. Arsène, Far, Zakaria, Hamidou, Davis…

Thank you.

"There's a divinity that shapes our ends/ Rough-hew them how we will." *Hamlet by Shakespeare.*

Ms. Imane. Ms. Soukayna

Ms. Imane, you helped me start the work; Ms. Soukayna, you helped me finish it. Thank you both.

"So long as men can breathe or eyes can see/ So long lives this, and this gives life to thee." *Sonnet 18 by Shakespeare*

My Year Group

I have had the singular opportunity to study with wonderful people. It's been one beautiful phenomenon. I wish I could mention all your names. Alas!

Ahmed, Hajar, Suléman, Mouad, Mansour, Khadija, Imane, Naima, Nassima, Btissam…

Aymériс, Namar, Germaine, Rougui,

Luke, Elizabeth, Mariata, Mike, Taweh

Béatrice, Adson

My Compatriots

I thank you guys for your support. You guys are amazing.

Dr. Keita, Dr. Samuel, Raphael

Thank you

And now

If I have erred or hurt anyone in the course of our encounters, either by commission or by omission, I, here, humbly plead for forgiveness for it was never my intention to hurt.

TABLES & FIGURES

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ABBREVIATIONS

I vowed to avoid abbreviations in this work to the best of my abilities. I have done that. But if any such is found in this work, it must have been an oversight. For that I'm sincerely sorry.

OUTLINE

INTRODUCTION

Since James Parkinson's findings on what he called "the shaking palsy", several advancements have been made. His findings on what we now know as Parkinson's disease have mostly stood the test of time [1]. Parkinson's disease, more than a movement disorder, involves several other axes of dysfunction including cognitive and autonomic dysfunction, as well as, sleep disorders, sensory impairment and neuropsychiatric manifestations [2–5]. The later is the focus of our research.

Parkinson's disease is a neurodegenerative disorder characterized essentially by the loss of dopaminergic neurons of the pars compacta of the locus niger of the basal ganglia [6, 7]. It is the second most common neurodegenerative disease after Alzheimer's disease [8]. It is characterized by hallmark motor symptoms such as bradykinesia, rest tremor and rigidity, which together constitute the extrapyramidal syndrome [9 –12].

The neuropsychiatric manifestations of Parkinson's disease are not only quite frequent, they could also antedate motor symptoms by several years [13]. Before motor symptoms appear, that is during the prodromal stage of the disease, the constellation of non motor symptoms may be the cause of errant diagnoses and several fruitless referrals [14, 15]. These non motor symptoms, especially the neuropsychiatric symptoms, have considerable impact on motor symptoms and quality of life, and considerably contribute to caregiver burden [16 – 20]. These symptoms could also be associated with medication [21, 22].

The incidence estimates of Parkinson disease range from 5 to over 35 new cases per 100,000 individuals yearly on a global scale [23]. The variation probably reflects differences in the demographics of the populations studied or in study methods. Parkinson's disease is rare before 50 years of age [23], but the incidence increases 5 to 10-fold from the 6th to the 9th decade of life [23 – 25]. The global prevalence, conservatively estimated at 0.3% overall, likewise increases sharply with age to over 3% in those over 80 years of age [26].

In Morocco, Parkinson's disease is estimated to be affecting 30 000 to 50 000 people, with an incidence of 4 000 new cases per year [27].

The number of people with Parkinson disease is expected to double [7] due to longer survival of patients with improved healthcare [28]. This has rather ominous socio-economic implications [29 – 34]. Mortality, however, remains high in patients with Parkinson's disease [35].

The disease is twice as common in men as in women in most populations [25, 36], with a few exceptions: one study in Japan found no difference or even a female predominance [37]. A protective effect of female sex hormones, a sex-associated genetic mechanism or sex-specific differences in exposure to environmental risk factors might explain this male predominance, although disparities in healthcare could also contribute. The incidence also seems to vary within subgroups defined by race, ethnicity, genotype or environment [38, 39]. Shared genetic factors, exposure to environmental pollutants, as well as lifestyle could explain the differences [40]. In fact, Parkinson's disease is more frequent in people exposed to pesticides and traumatic brain injury, and lower in smokers and caffeine users [41].

Progress has been made in understanding the neuropathology of Parkinson disease and its progression throughout the nervous system, as well as the molecular and neurophysiological mechanisms and perturbations underlying the disease and its symptoms. This has made it possible to synthesize efficacious therapies targeting specific points in the disease process. Of especial mention is the dopamine replacement therapy which comes as the first line of treatment in Parkinson's disease. Also, innovatively conceived is the biotechnological approach to treatment, deep brain stimulation, which extends the therapeutic arsenal to surgical dimensions. Parkinson's disease, therefore, enjoys that singular place of being the first and still unparalleled example of a neurodegenerative disease that can be effectively managed, leading to sustained symptom control and quality of life up to decades after disease onset [42].

Despite these advancements in the treatment of Parkinson's disease, most patients express some level of dissatisfaction at outcomes. In the particular case of our patients, there are several complaints of non motor symptoms despite an effective control of motor symptoms. This has resulted in frustration among patients and their caregivers, and influences attitudes toward the disease.

Our hypothesis is that non motor symptoms, especially neuropsychiatric manifestations, are quite frequent in our patients. These manifestations also have an adverse impact on the quality of life of our patients.

The primary aim of our study, therefore, is to

- determine the prevalence of neuropsychiatric manifestations in Parkinson's disease
- determine their impact on the quality of life of our patients

And, secondarily, to

- investigate the fluctuations of these manifestations
- evaluate the response to treatment of these manifestations
- investigate the risk factors favoring the occurrence of these manifestations

PATIENTS AND METHODS

I. Methods

1. Study Design

1.1. Study type

- A prospective, single center, descriptive and analytical study

1.2. Study duration

- Conducted over a period of 1 year from March 2018 to March 2019

1.3. Setting

- Specialized Movement Disorder consultation, Department of Neurology, Arrazi Hospital, Mohammed VI University Teaching Medical Center

1.4. Patients

a. Criteria of inclusion

- All patients followed up in the Department of Neurology during the period of study diagnosed with idiopathic Parkinson's disease by a board-certified Neurologist in the department
- The diagnosis of Parkinson's disease was based on the UK Parkinson's Disease Society Brain Bank Criteria[12] (Annex IV, 1)
- Diagnosis should have been made at least 6 months prior to the research

b. Criteria of exclusion

- Patients not willing to take part in the study

1.5. Tools

- An initial structured interview was conducted to gather information pertaining to patient history, age, age of onset, duration of disease, and treatment
- A set of two questionnaires was administered to the patients and their caregivers during their appointment with a neurologist in the department
  1. A 10-item version of the Neuro-Psychiatric Inventry (NPI) administered to patients' caregivers by a trained interviewer from the department **(Annex IV, 2)**
     - Positive responses were probed with structured questions focusing on specific features of the neuropsychiatric symptom. The informant rated the frequency of each symptom on a scale from 1 to 4, and the severity of the symptom on a scale from 1 to 3. A composite score, defined as the product of frequency and severity, yielding a score ranging from 1 to 12 for each item, was used in the analysis. A caregiver distress item was also included, where the caregiver was requested to score the level of emotional distress they experienced due to each symptom (level of distress: not at all, 1; minimal, 2;moderate, 3; severe, 4; very severe or extreme distress, 5).
  2. A self-report questionnaire administered directly to patients, and where necessary, the help of the caregiver was sought. This questionnaire evaluated the response to treatment of a set of neuropsychiatric symptoms **(Annex IV, 3)**
- A third interview was conducted either in person, or over the phone for those living far away who could not come in, and involved the administration of the Parkinson's Disease Quality of Life measure 8-item version(PDQ-8) directly to patients, and where necessary, the help of the caregiver was sought **(Annex IV, 4) (FIG 1)**
- The PDQ-8 aggregate score was found by calculating the sum of the score from each of the eight domains; this sum was then expressed as a percentage of the total maximum score possible:

$$\frac{\text{Score from each domain} \times 100}{\text{Maximum score from each domain} \times 8}$$

- Higher scores imply worse quality of life (QoL) outcomes.
- A Cronbach $\alpha \geq 0.7$ was considered an acceptable measure of internal reliability.

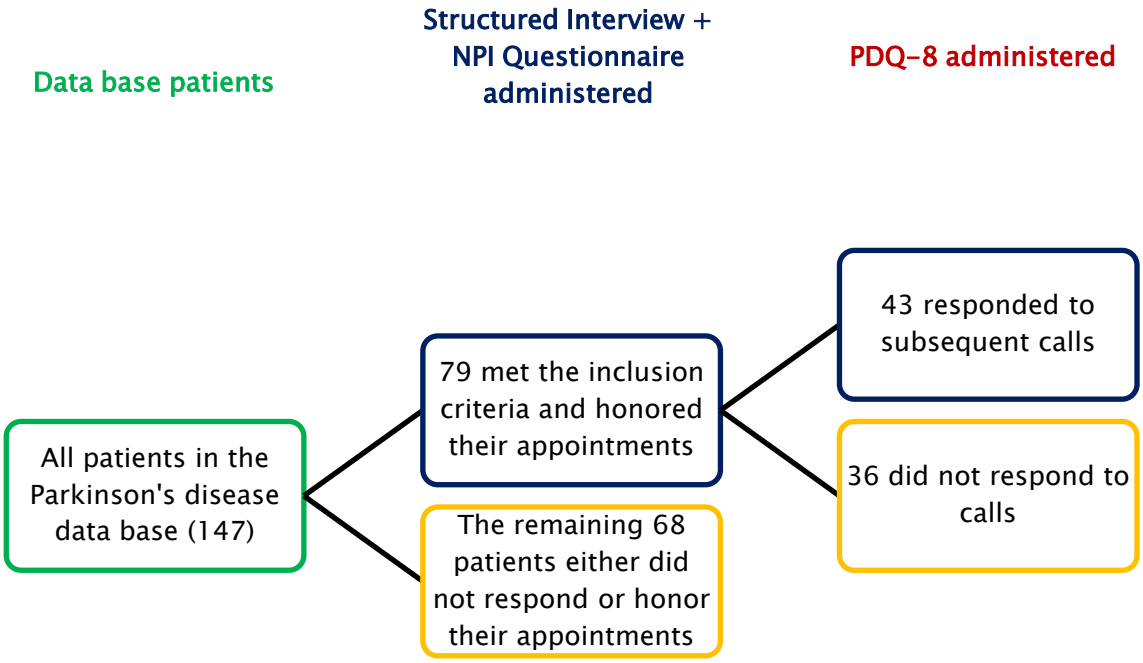

Figure 1. Flow chart representing the recruitment process of our ascertainment cohort

2. Statistical Analysis

- Data were first reported on a questionnaire sheet and later transferred on the SPSS program
- Descriptive and multivariate analyses were conducted using the SPSS software version 21 for Windows (SPSS Inc., Chicago, III., USA)
- For descriptive analysis, sample size, rates, ranges, means and standard deviations (SD) were calculated for the various variablesfrom each interview,first for the general sample
- Variables studied included 10 items on the NPI scale (Delusions, Hallucinations, Aggressivity, Depression, Anxiety, Euphoria, Apathy, Disinhibition, Irritability and Sleep disorders), and 7

items on the treatment response questionnaire (Depression, Anxiety, Panic attacks, Apathy, Hallucinations, Impulse Control Symptoms and Cognitive impairment)

- Next, for each variable, the group of patients presenting a symptom was examined based on gender, age groups, onset groups, and duration groups
  - As to gender, the sample was dichotomized into female and male subgroups
  - As to age groups and onset groups, an arbitrary grouping created the following class intervals: <40, 40 – 49, 50 – 59, 60 – 69, ≥70 year age groups
  - As to duration of disease groups, an arbitrary grouping created the following class intervals: <5, 5 – 9, 10 – 14, ≥15 year duration groups
- Student's t-test was used for comparisons of normally distributed continuous data and $\chi 2$ test forcategorical variables
- To test whether patients with different NPI scores differed on demographic and clinical variables, comparisons of continuous data were carried out using one-way analysis of variance. In case of rejection of the nul hypothesis, the post-hoc Scheffé multiple comparison procedure was used to determine which group means were different from each other
- Bivariate correlation was performed where appropriate. The Pearson r was determined
- In order to identify predictors of worse outcomes on quality of life, a multivariate analysis was performed using a stepwise logistic regression, submitting all covariates that showed statistical significance
- A p-value <0.05 was considered significant
- We indicate that in this study, the tools used only allow for identification of symptoms, and not for specific diagnoses. Hence, the use of terms such as 'Depression', 'Anxiety', etc, should be understood as 'depression symptoms' and 'anxiety symptoms' respectively, and not specific diagnoses of depression and anxiety.

3. Ethical Considerations

- The research proposal was studied and approved by the Faculty Thesis Committee
- All patients and their caregivers involved in the research were informed once they met the criteria for inclusion and gave verbal consent to their involvement in the study

RESULTS

I. General Findings

1. Gender

- The study comprised 79 patients in all, 36 of whom were females, representing 45.57% of the sample; and 43 were males, representing 54.43% of the sample. **(FIG 2)**
- The sex ratio was 1.19.

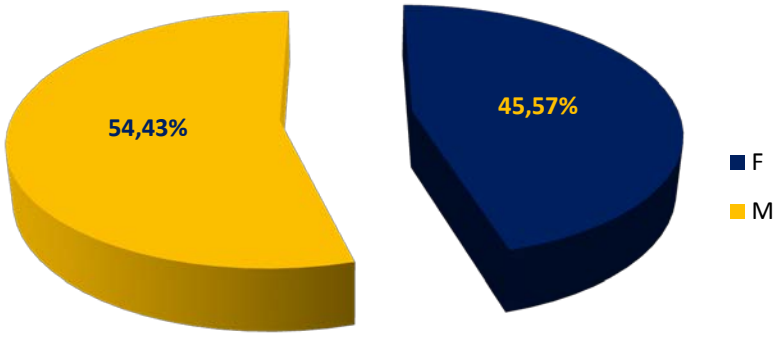

Figure 2: Distribution of Patients based on Gender

2. Place of residence

- Up to 64.56% of our patients lived in rural areas. **(FIG 3)**

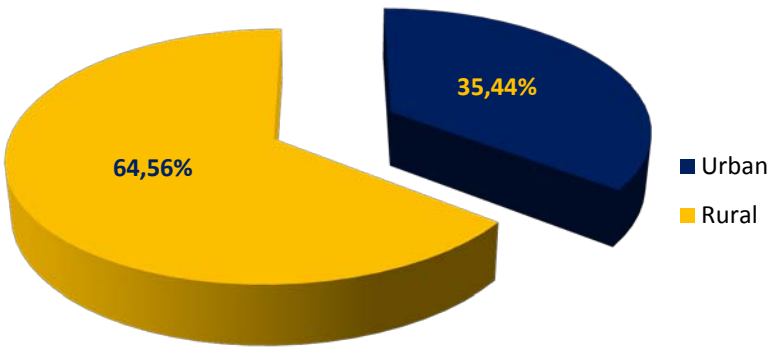

Figure 3 : Distribution of patients based on residence

3. Healthcare insurance

- Only 15.19% of patients had healthcare insurance. **(FIG 4)**

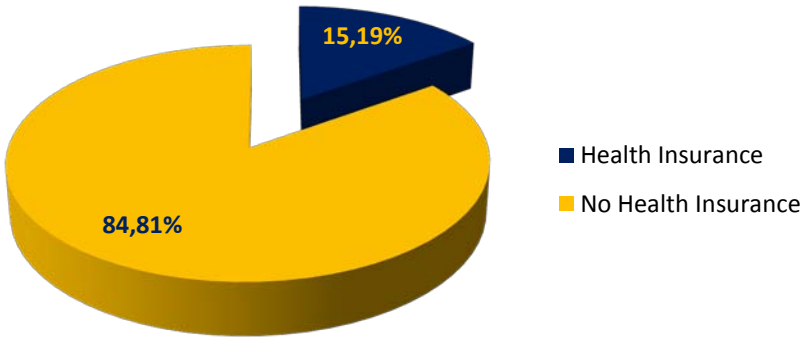

Figure 4 : Distribution of patients based on whether or not they have health insurance

4. Patient history

- Up to 43.85% of our patients were followed up for some documentedmedical condition other than Parkinson's disease at the time of diagnosis**. (FIG 5)**

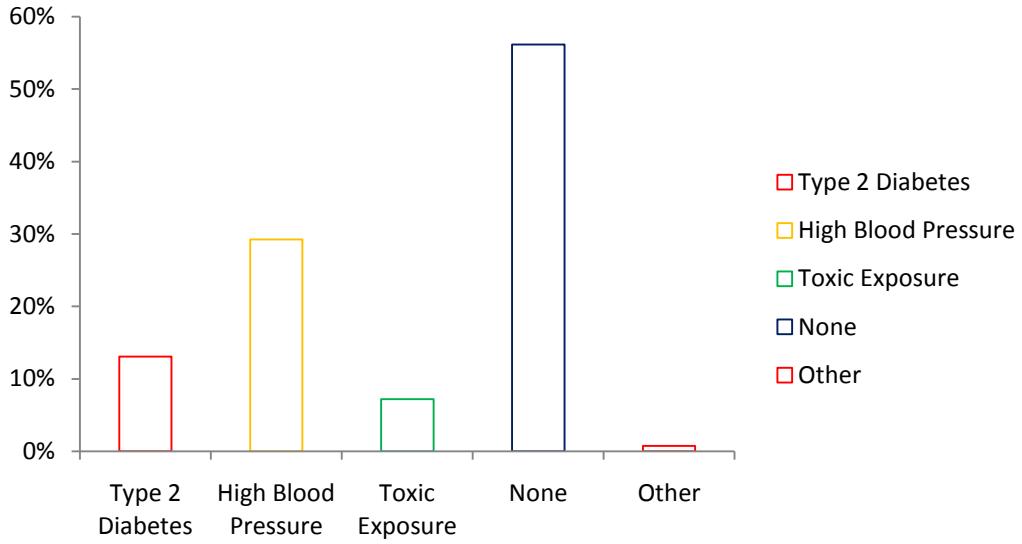

Figure 5 : Distribution of Findings on Patient History

5. Age, Age of onset, Disease duration

- The ages of the patients ranged from 28 to 78 years. A mean age of 59.04 years (SD = 9.43) was found in the sample.
- Patients aged 60 – 69 years were the most frequent with a relative frequency of 43%, whereas the least frequent age group was patients aged ≥ 70 years who had a frequency of 10.10%. **(FIG 6)**

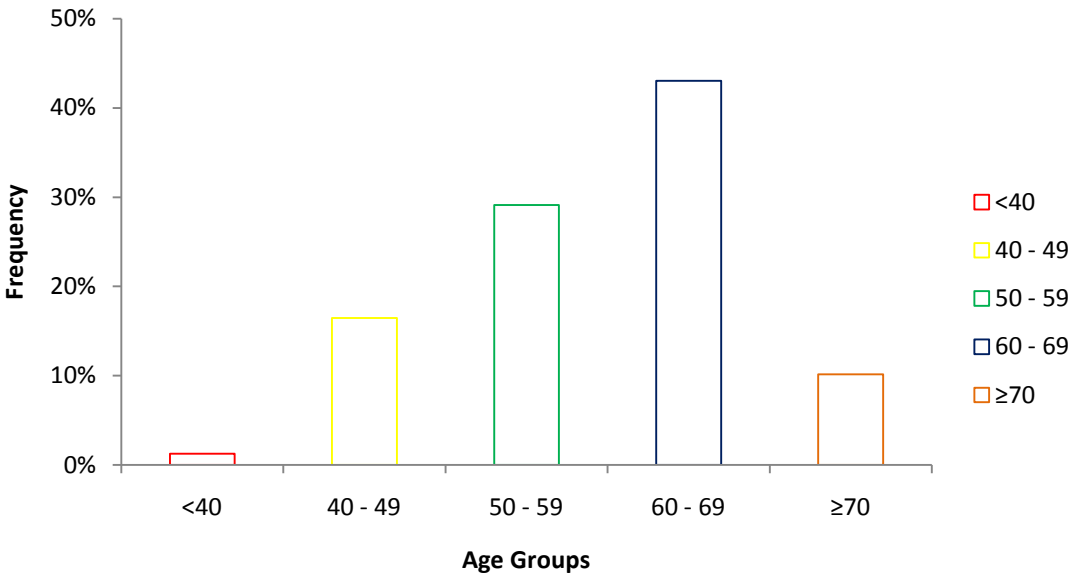

Figure 6 : Distribution of Patients Based on Age Groups

- The age of onset ranged from 20 to 73 years. The mean age of onset was 52.57 years (SD = 9.91).
- Up to 43.00% of our sample had an age of onset within the 50 – 59 year range, while only 2.50% of patients had an age of onset of 70 years and above. **(FIG 7)**

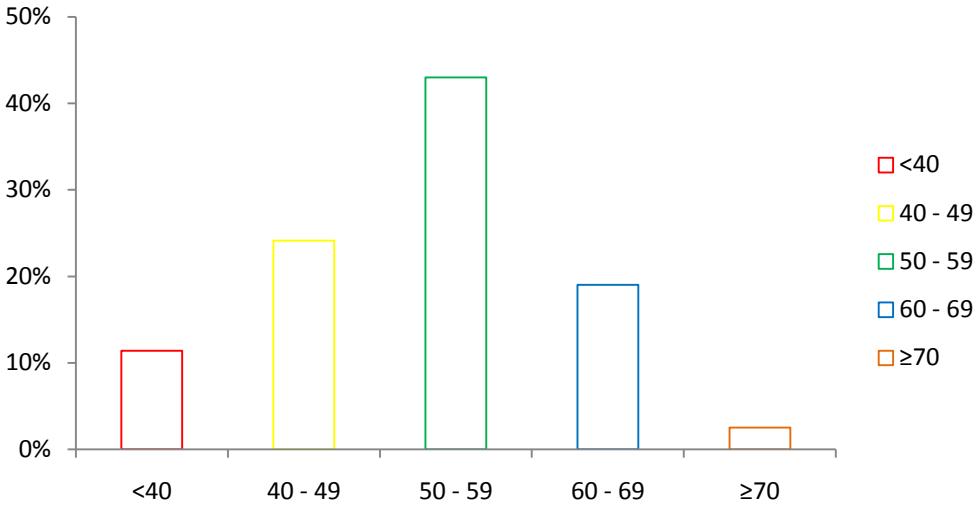

Figure 7 : Distribution of Patients Based on Age of Onset Groups

- Patients with age of onset < 50 years represented 35.44% of our sample. **(FIG 8)**

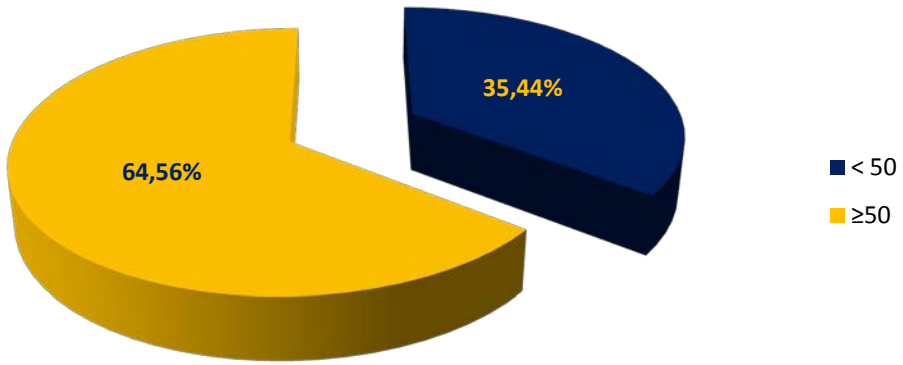

FIGURE 8 : Distribution of Patients Based on Onset before or after 50 years

- The duration of illness ranged from 6 months to 16 years. On average, the mean duration of illness was 6.52 years (SD = 3.81).

- Patients with a disease duration of 5 – 9 years were the most frequent, with a frequency of 44.3%, whereas patient with a disease duration ≥ 15 years were the least frequent with a frequency of 6.3%. **(FIG 9)**

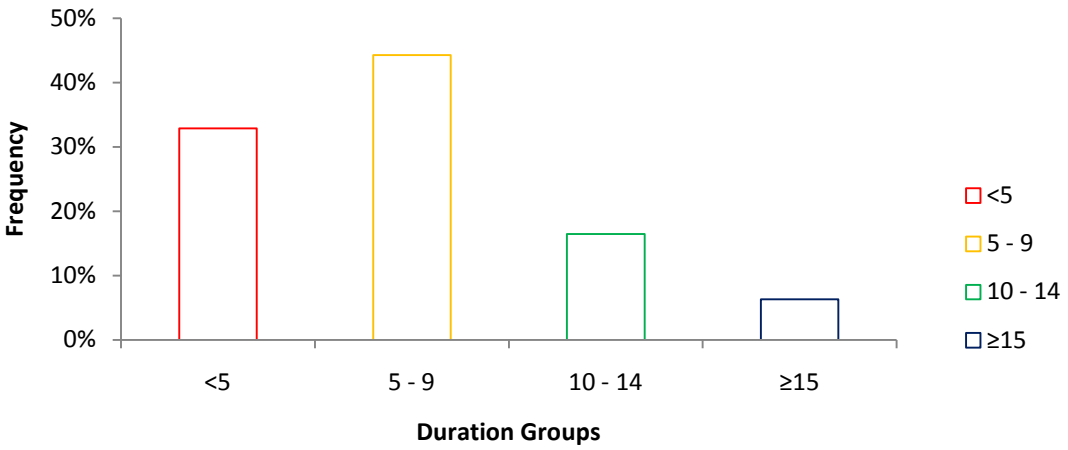

Figure 9 : Distribution of Patients Based on Duration Groups

- No difference was observed across genders in terms of age (p = 0.44), age of onset (p = 0.24), and duration (p = 0.30).

6. Clinical symptoms

- Out of the 79 patients evaluated with the NPI questionnaire, 94.94% presented at least one symptom. **(FIG 10)**

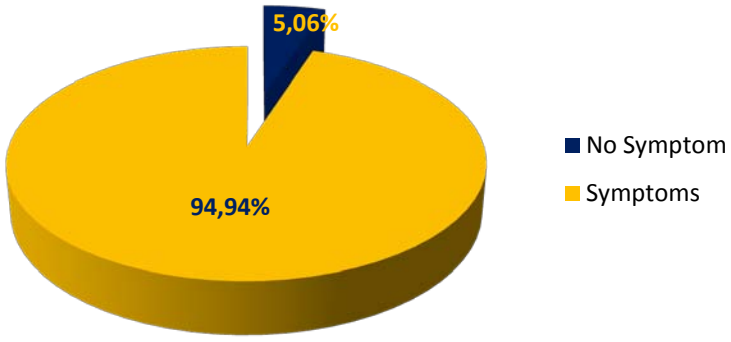

Figure 10 : Distribution of Symptoms in our Patients

- The most frequent symptoms were depression (77%), irritability (67%), anxiety (57%) and sleep disorders (52%). The least frequent were apathy (16%), delusions (14%), and hallucinations (14%). **(FIG 11)**

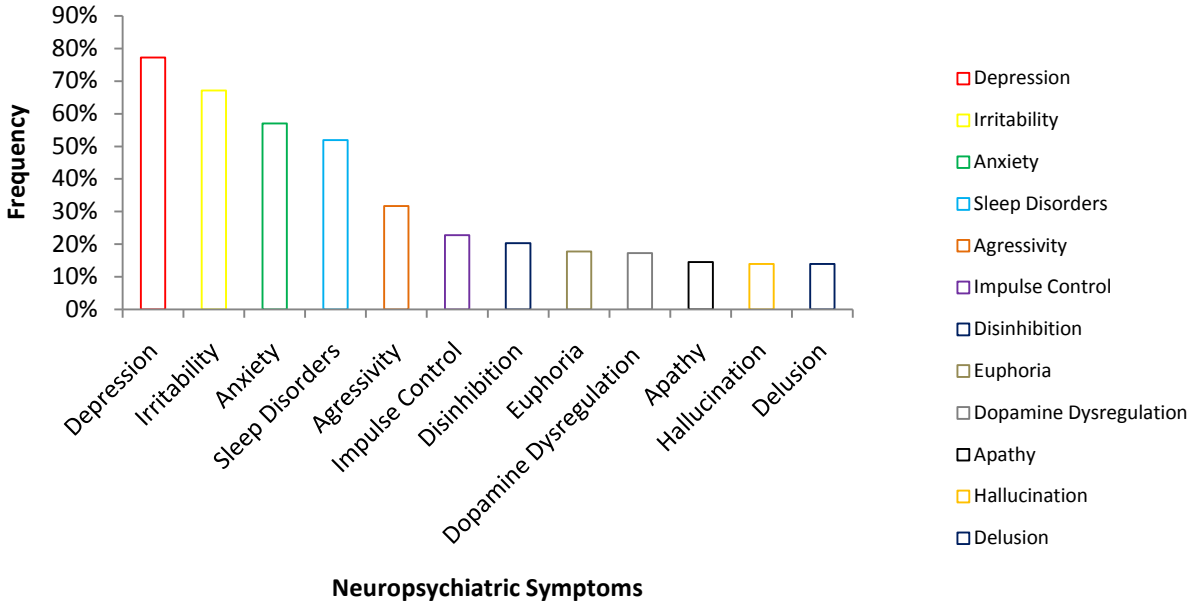

Figure 11 : Prevalence of Neuropsychiatric Symptoms

- Among patients reporting symptoms, the highest scores were recorded for sleep disorders depression, and anxiety. **(FIG 12)**

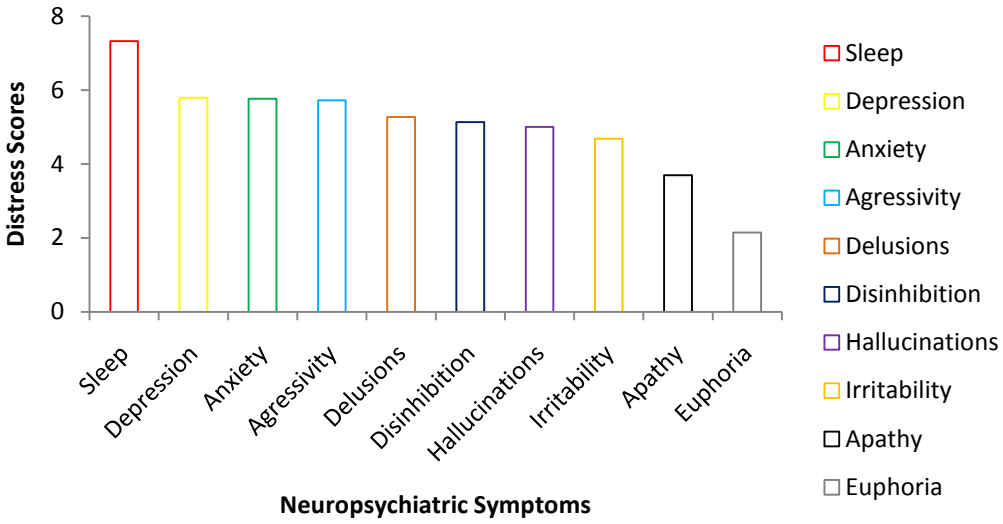

Figure 12 : Distress Scores for Neuropsychiatric Symptoms

- Of the patients reporting symptoms, 90.58% of them presented more than one symptom.
- The majority of patients reported 2 to 6 symptoms simultaneously. **(FIG 13)**

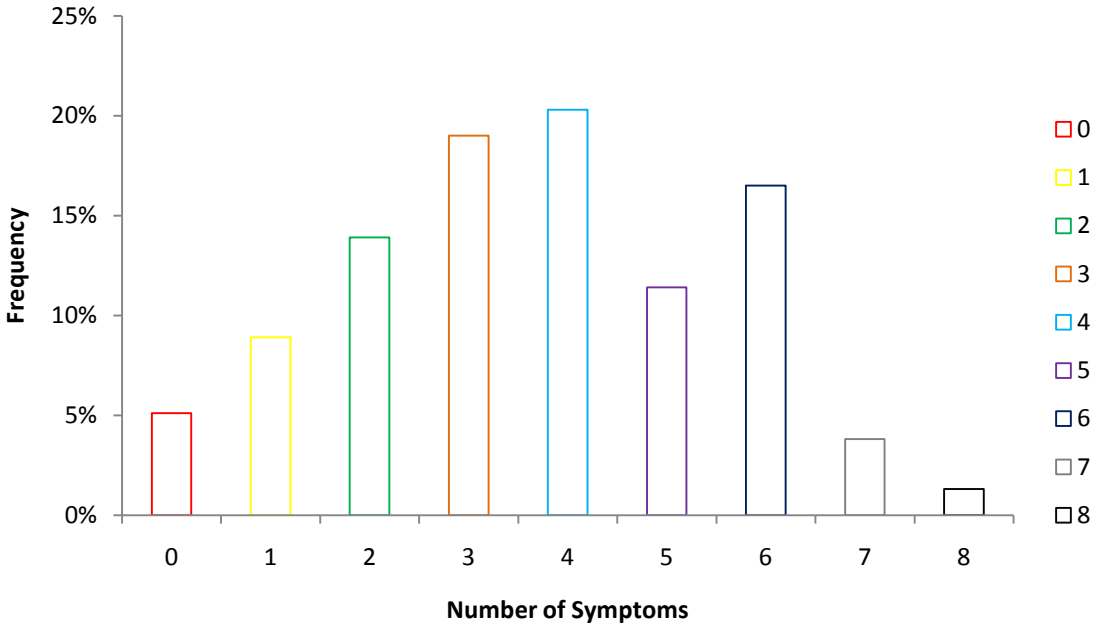

Figure 13 : Distribution of Number of Symptoms Reported in Patients

- The mean number of symptoms present was 3.67 (SD = 1.90); 4.36 (SD = 1.64) in the female group, and 3.09 (SD = 1.93) in the male group.
- A statistically significant difference was observed across genders with females reporting more symptoms than males (p = 0.02). **(FIG 14)**
- The mean total score was 22.57 (SD = 16.61) in the general sample, 26.69 (SD = 16.71) in the female group, and 19.12 (SD = 15.89) in the male group.
- A statistically significant difference was observed across genders with females reporting higher mean total scores than males (p = 0.04). **(FIG 14)**
- The mean PDQ-8 score was 43.11 (SD = 22.10), and ranged from 3.13 to 90.63.
- On the PDQ-8, female patients reported a statistically higher mean of 52.78 (SD = 19.99) than males 34.82 (SD = 20.78); p = 0.009. **(FIG 14)**

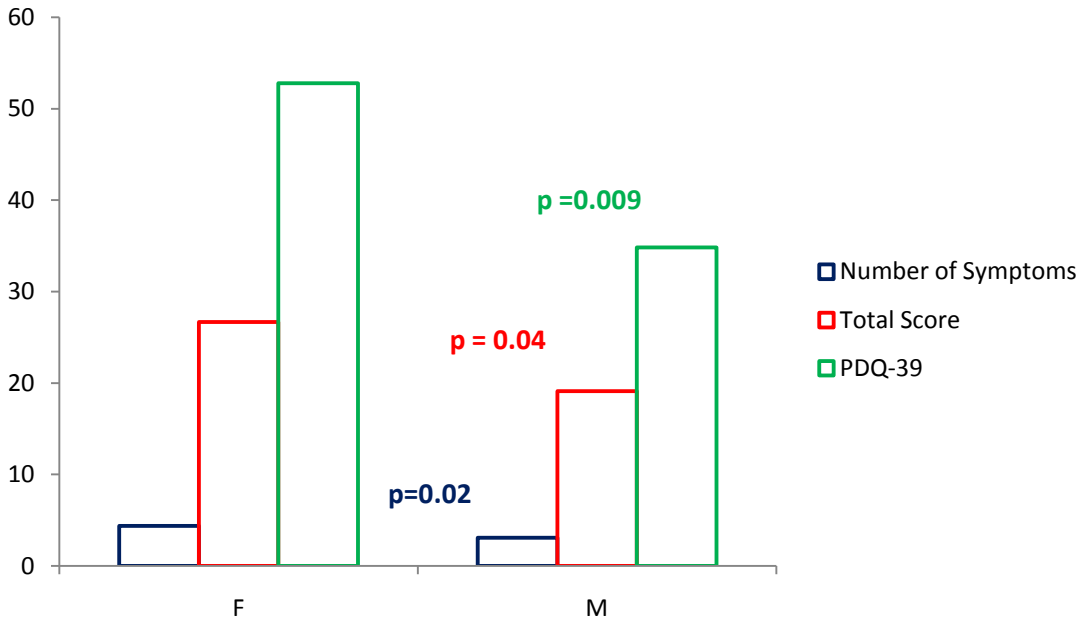

Figure 14 : Comparison of Number of Symptoms, Total NPI Score, and PDQ-8 Score in Female and Male Patients

TABLE I : Summary of Patient and Caregiver Distress NPI Scores (N = 79)

	All Patients				Patients showing symptoms					
	Item score		Care giver distress score		Proportion with non-zero score	Item score		Care giver distress score		
NPI Item	Mean	SD	Mean	SD	n(%)	Mean	SD	Mean	SD	n(% of patients with symptom)
Delusions	0.73	2.27	0.33	1.23	11(13.92%)	5.27	3.74	4.33	1.63	6(54.55%)
Hallucinations	0.7	1.9	0.30	1.14	11(13.92%)	5.00	2.15	4.00	1.55	6(54.55%)
Aggressivity	1.81	3.23	0.57	1.60	25(31.65%)	5.72	3.26	5.00	0	9(36.00%)
Depression	4.47	3.32	1.47	2.14	61(77.22%)	5.79	2.56	4.00	1.49	29(47.54%)
Anxiety	3.28	3.91	1.19	2.00	45(56.96%)	5.76	3.54	4.09	1.35	23(51.11%)
Euphoria	0.38	0.88	0.38	1.12	14(17.72%)	2.14	0.77	3.33	1.12	9(64.29%)
Apathy	0.61	1.71	0.22	0.96	13(14.46%)	3.69	2.56	4.25	0.96	4(30.77%)
Disinhibition	1.04	2.46	0.47	1.42	16(20.25%)	5.13	3.01	4.63	0.74	8(50.00%)
Irritability	3.14	3.03	1.43	2.14	53(67.09%)	4.68	2.54	4.19	1.33	27(50.94%)
Sleep	3.8	4.26	1.20	2.04	41(53.90%)	7.32	3.01	4.13	1.46	23(56.10%)

- A low correlation was observed between duration of disease and number of symptoms (r = 0.26, p = 0.02).
- No correlation was observed between total score and age (p = 0.59), and age of onset (p = 0.29), and duration (p = 0.15).
- No correlation was found between L-dopa dose and age (p = 0.67), or total score (p = 0.085). The correlation between dose and duration of disease approached significance (p = 0.06).
- No difference was found across genders with respect to response to treatment.
- A correlation was found between PDQ-8 scores and depression (p=0.046); the association with aggressivity approached significance (p=0.073).

II. Specific Findings

1. Depression

1.1. Prevalence

- Depression was found in 61 patients, that is 77.22% of our sample. **(FIG 15)**

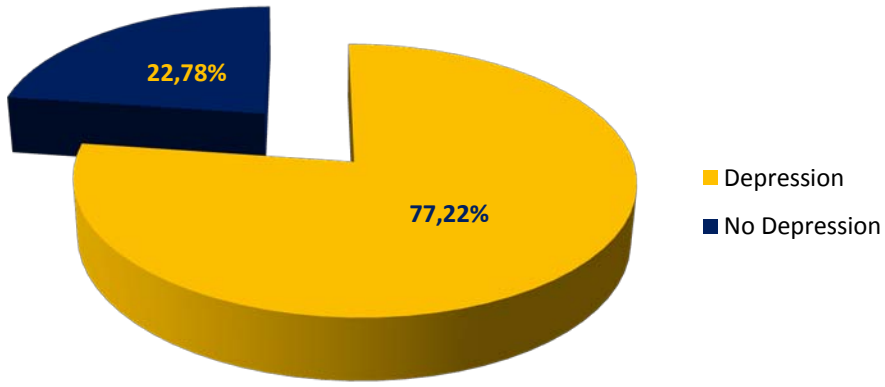

Figure 15 : Distribution of Depression in Our Patients

- With respect to gender, 34 patients were females, that is 94.44% of the female patients; and 27 were males, that is 62.79% of male patients. **(FIG 16 & 17)**
- There was a statistically significant difference in the distribution of depression in terms of gender ($\chi 2 = 11.15$, df = 1, p = 0.01, $\varphi = -0.376$).

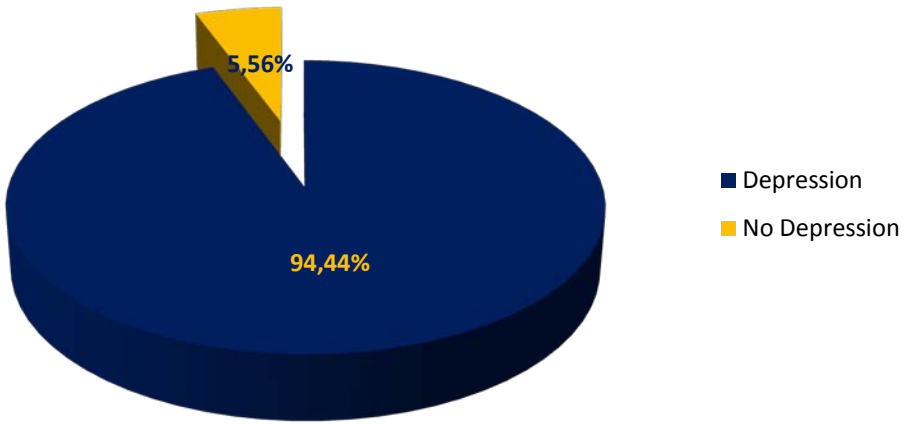

Figure 16 : Distribution of Depression in Females

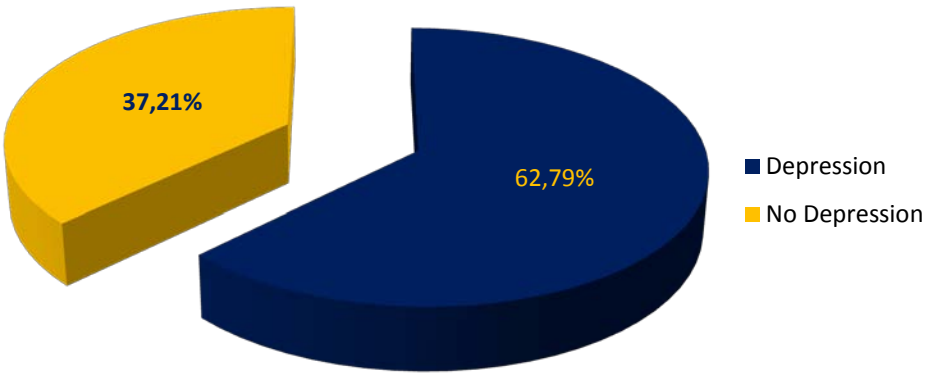

Figure 17 : Distribution of Depression in Males

1.2. Score

- In the set of patients with depression, the average score was 5.79 (SD = 2.56).
- The difference in distress score across genders did not reach the level of statistical significance (p=0.567). **(FIG 18)**

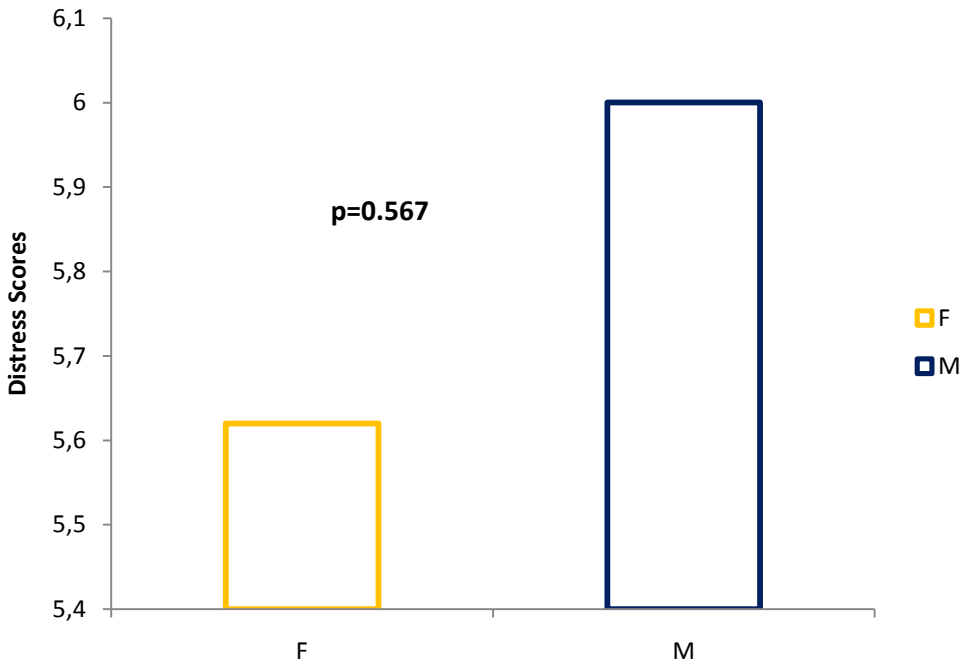

Figure 18 : Distribution of Distress Scores in Males and Females

1.3. Age of Onset, Duration

- The mean age of onset of patients reporting depression was 51.18 years (SD = 9.40) whereas patients without depression had a mean age of onset of 57.28 years (SD = 10.40). A statistically significant difference was found between the two (p = 0.03).
- The mean duration of disease in patients reporting depression was 7.23 years (SD = 3.89). There was a statistically significant difference between patients reporting depression and those without depression in terms of duration, with patients reporting depression presenting a longer duration of disease (p < 0.0001).

- Depression was most prevalent in patients with disease duration of 10 years and above (100%) and least prevalent in patients with disease duration less than 5 years (53.85%). **(FIG 19)**

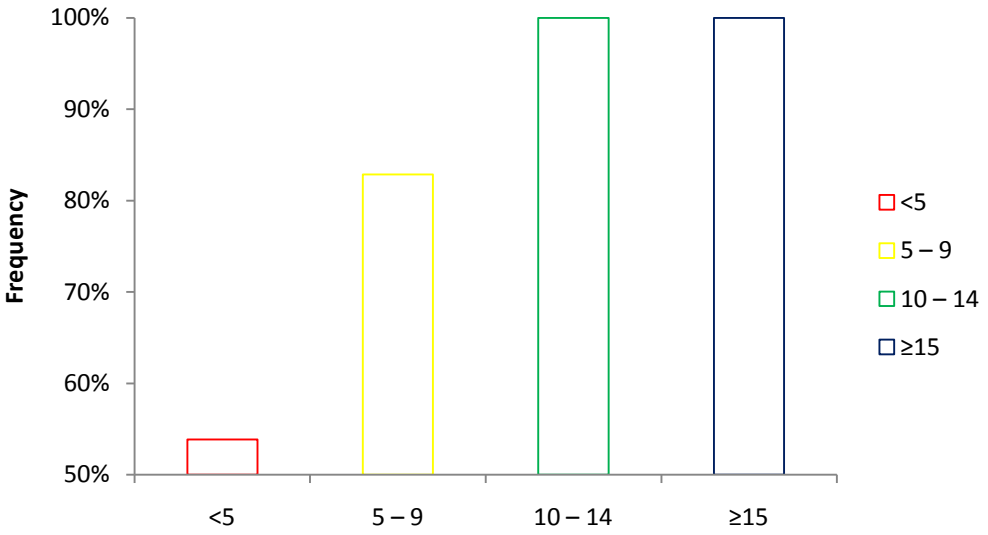

Figure 19 : Distribution of Depression in Duration Groups

- The highest distress score was recorded in patients having a disease duration less than 5 years. **(FIG 20)**

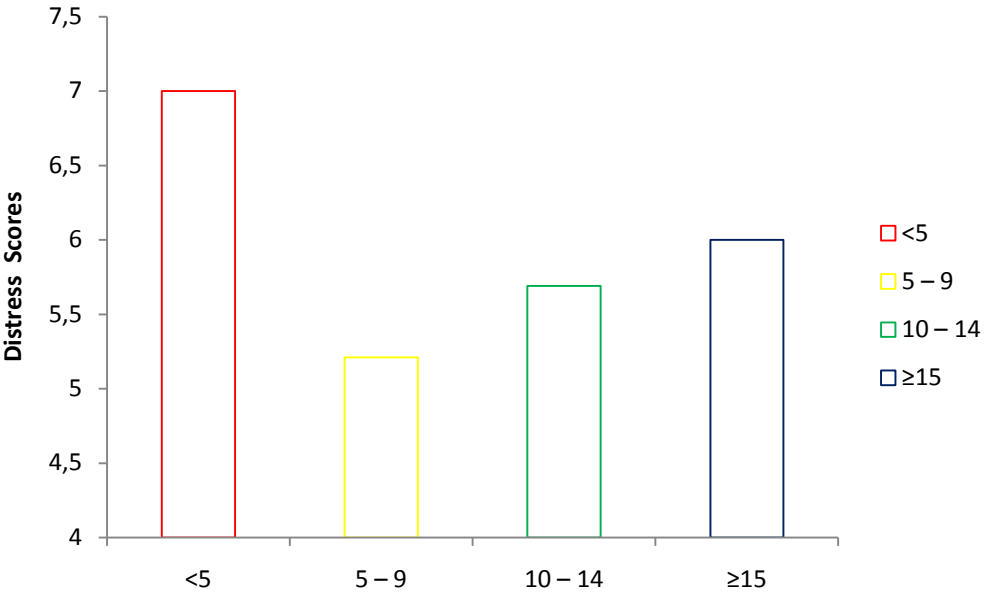

Figure 20 : Distribution of Patients Based on Age of Onset Groups

- There was no correlation between depression distress score and age (p=0.233).
- FIG 21 below shows that patients reporting depression have a younger age of onset and a longer duration of disease than patients without depression.

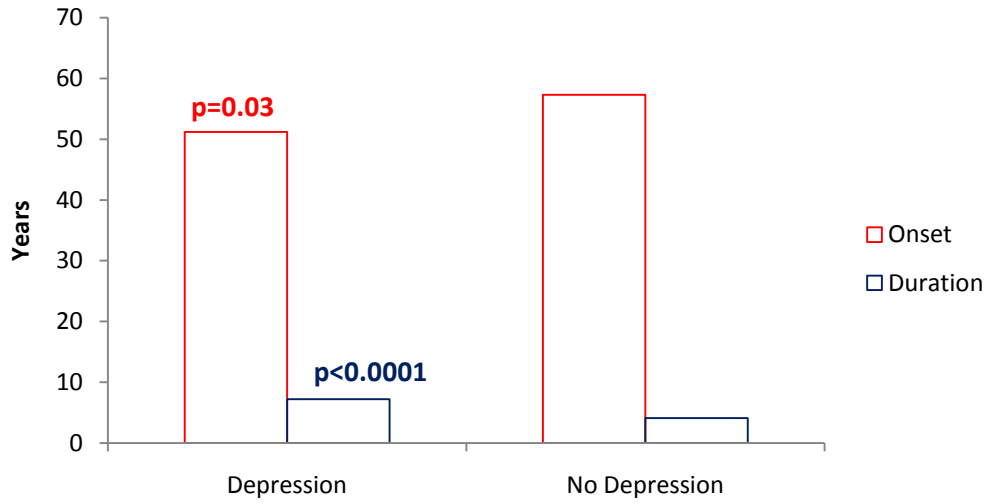

Figure 21: Comparison of Onset and Duration in Patients with and those without Depression

1.4. Other NPI items

- All patients experiencing delusions (100%) also reported depression.
- In terms of correlation, a moderate positive correlation was found between depression and anxiety($r = 0.57$, $p < 0.0001$).

1.5. Caregiver Distress

- Up to 47.54% of cases of depression caused some level of distress for caregivers.
- The mean score was 4.00 (SD=1.49) and ranged from 1 to 5. The majority (17) of caregivers reported a maximum distress score of 5. That is 17 out of 29 caregivers, or 58.62% of those who reported some level of distress said it was extremely distressing.
- Breaking our findings down into gender groupings, we found that 19 of the 29 caregivers (65.51%) catered for female patients. That is 19 out of 34 females reporting depression, or 55.88%. The mean score was 4.11 (SD=1.37) with 11 out of the 19 (57.89%) reporting extreme distress.

- The remaining 10 caregivers (34.48%) catered for male patients. That is 10 out of 27 males reporting depression, or 37.04%. The mean score was 3.80 (SD=1.75), with 6 out of the 10 (60.00%) reporting extreme distress. **(FIG 22 & 23)**

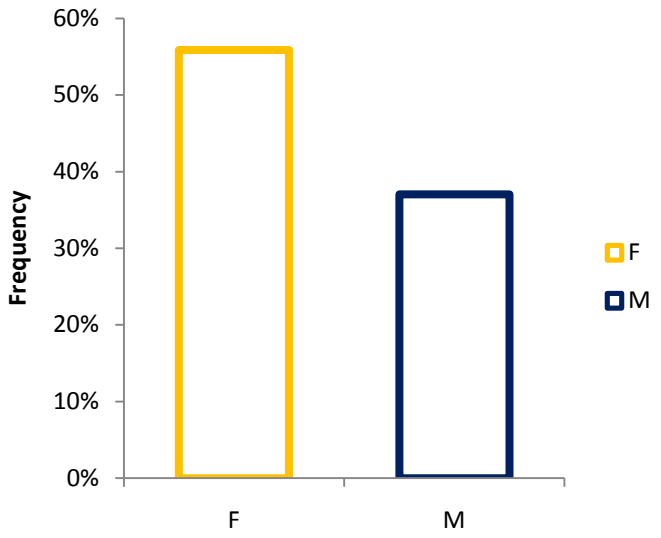

Figure 22 : Distribution of Caregiver Distress based on Gender of Patients

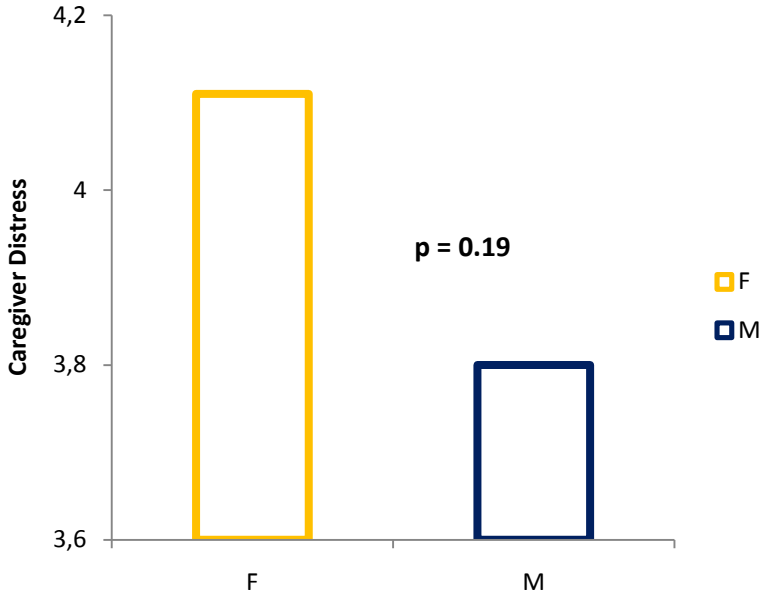

Figure 23 : Distribution of Caregiver Distress Scores based on Gender

- Caregiver distress score was better correlated withthe depression in male patients than that in female patients. ($r = 0.54$, $p < 0.0001$ vs.$r = 0.38$, $p < 0.0001$)

1.6. Response to Treatment

- Of patients reporting depression, 87.93% reported symptoms only during the off-state showing improvement during the on-state. The remaining 12.07% reported depression during the off and on states. **(FIG 24)**
- There was no statistically significant difference between the male and female groups with respect to response to dopamine therapy ($\chi 2$=0.36, df = 1, p = 0.55).

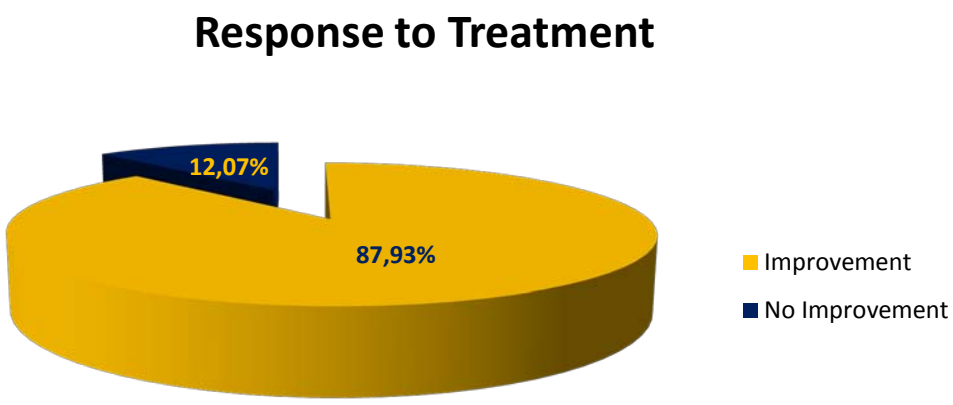

Figure 24 : Distribution of Response to L-Dopa Treatment

- Patients who responded to treatment did not differ from those without improvement of symptoms in age (p= 0.375), age of onset (p= 0.178), duration (p= 0.144), and L-dopa dose (p= 0.794).

- Patients reporting depression received higher doses of L-dopa than those without depression (p = 0.011). **(FIG 25)**

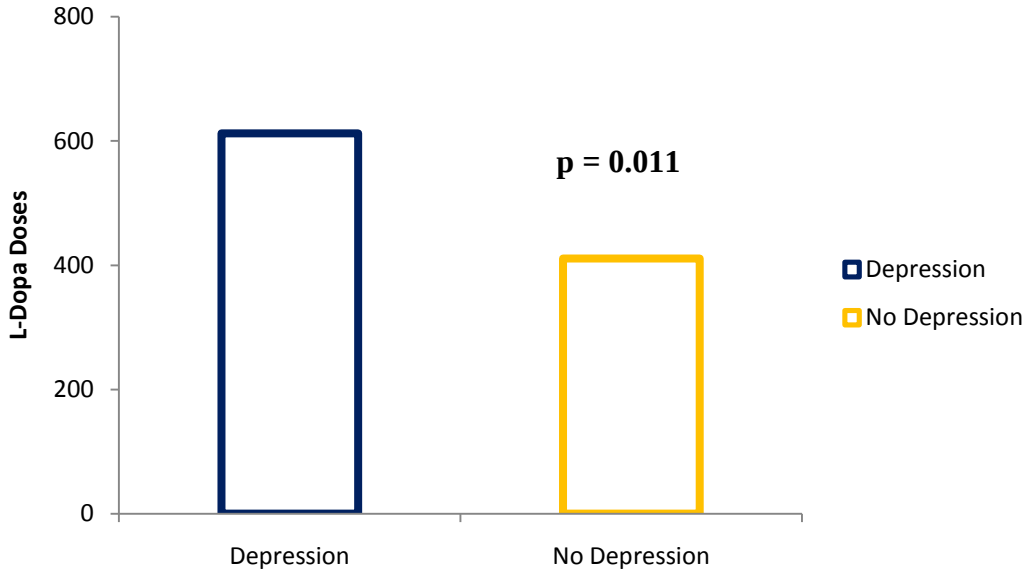

Figure 25 : Comparison of L-Dopa Dose in Depressed and Non Depressed Patients

1.7. Impact on Quality of Life

- Depression distress scores were correlated to worse QoL outcomes (p=0.046).

2. Anxiety

2.1. Prevalence

- Anxiety was reported in 56.96% of our sample. **(FIG 26)**

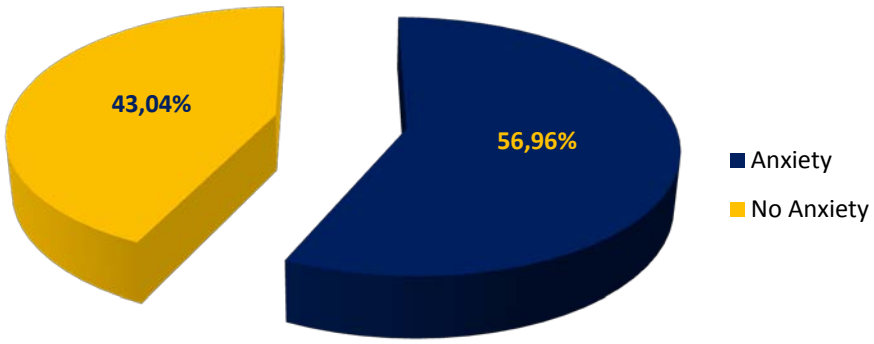

Figure 26 : Distribution of Anxiety in the Sample

- Anxiety was found in 66.67% of the female sample, and 48.83% of the male sample. Males and females did not differ significantly in the distribution of anxiety ($\chi 2 = 2.54$, df=1, $p > 0.05$). **(FIG 27 & 28)**

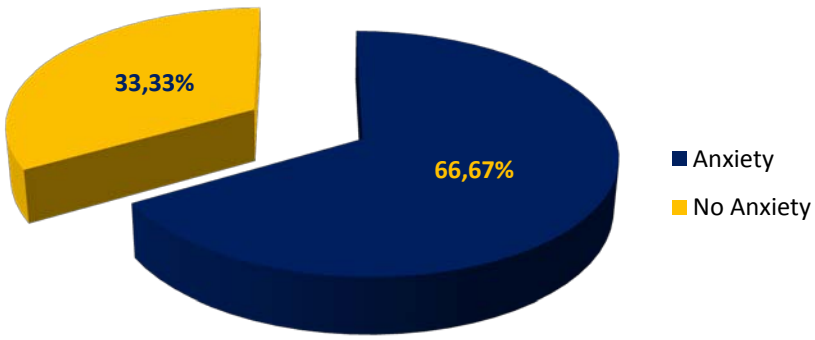

Figure 27 : Distribution of Anxiety in Females

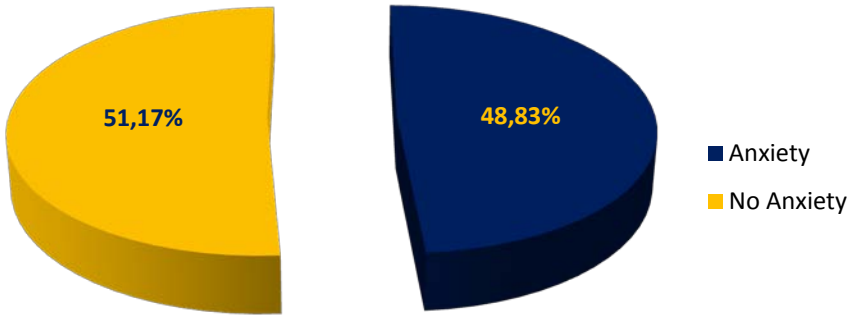

Figure 28 : Distribution of Anxiety in Males

2.2. Scores

- In the set of patients reporting anxiety, the average score was 5.76 (SD = 3.54).
- There was no statistically significant difference between the mean distress score across genders (p=0.812). **(FIG 29)**

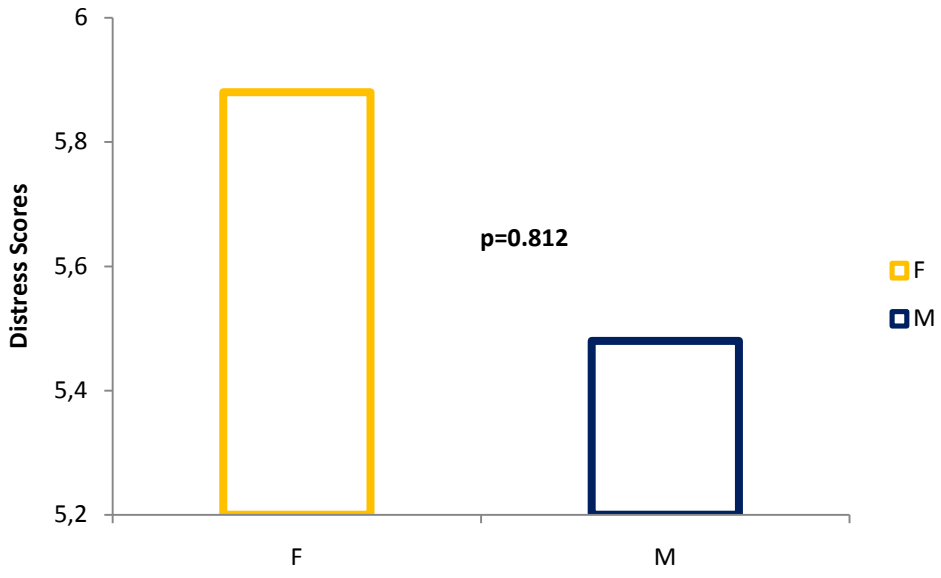

Figure 29 : Comparison of Distress Scores in Males and Females

2.3. Age of Onset, Duration

- The mean age of onset of patients reporting anxiety was 52.40 years (SD= 10.15); and the mean duration of disease was 6.51 years (SD = 3.67).
- There was no statistical difference between patients reporting anxiety and those without anxiety in terms of age, age of onset, and duration. **(FIG 30)**

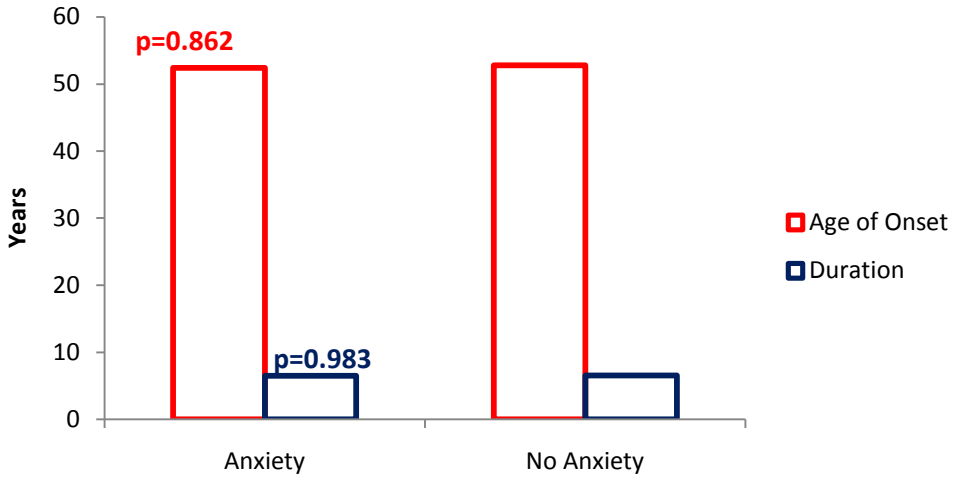

Figure 30 : Comparison of Onset and Duration in Patients with and those without Anxiety

- Anxiety was most frequent in patients with age at onset of 70 years and more (87.5%), and was least reported in patients in the 40 – 49 years group (46.15%). **(FIG 31)**

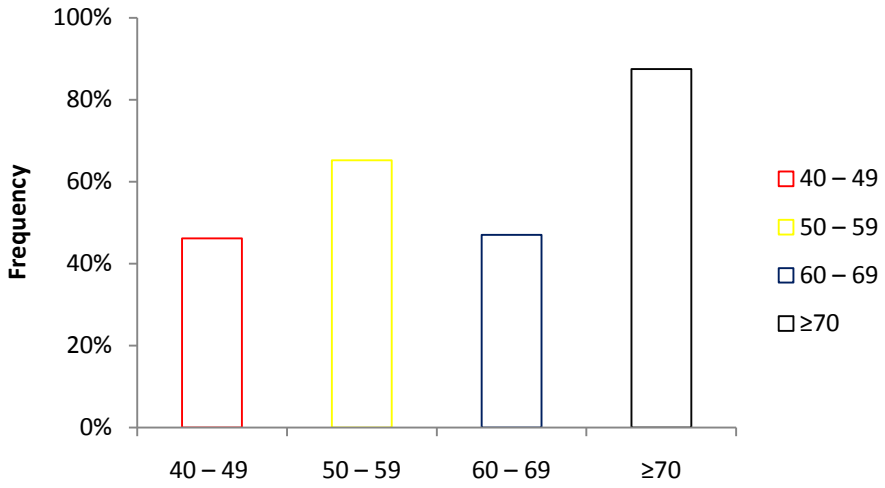

Figure 31 : Distribution of Anxiety in the Age of Onset Groups

- The scores for anxiety was least (3.33, SD=2.58) in patients with age at onset of 40 – 49 years, and highest (6.13, SD=3.96) in patients in the 50 – 59 years group. **(FIG 32)**

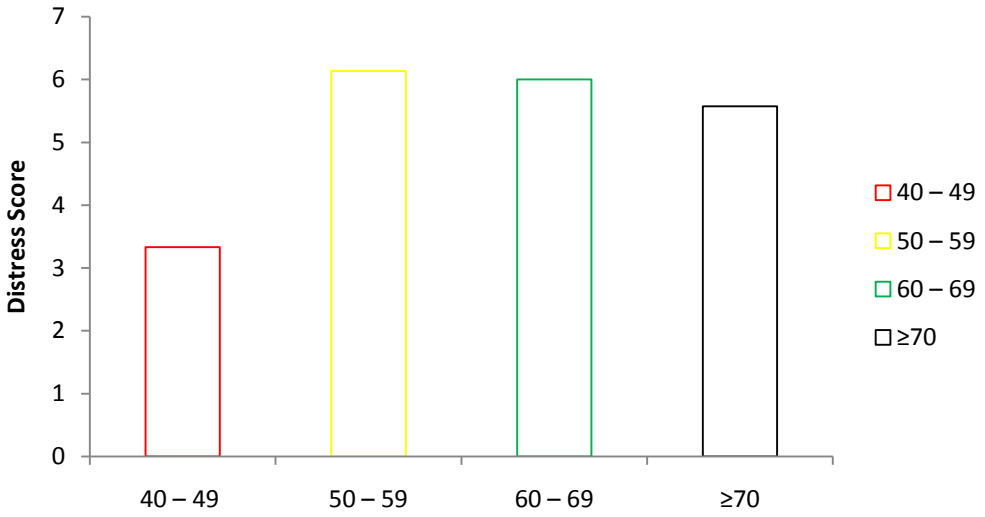

Figure 32 : Distribution of Distress Score in Age of Onset Groups

- The only patient aged less than 40 years also reported anxiety with the maximum score of 12.
- Our study found no correlation between anxiety distress scores and age of patients.
- Patients with disease duration of at least 15 years had the least frequency of anxiety (40%), while patients with disease duration from 10 to 14 years had the highest frequency (69.23%). **(FIG 33)**

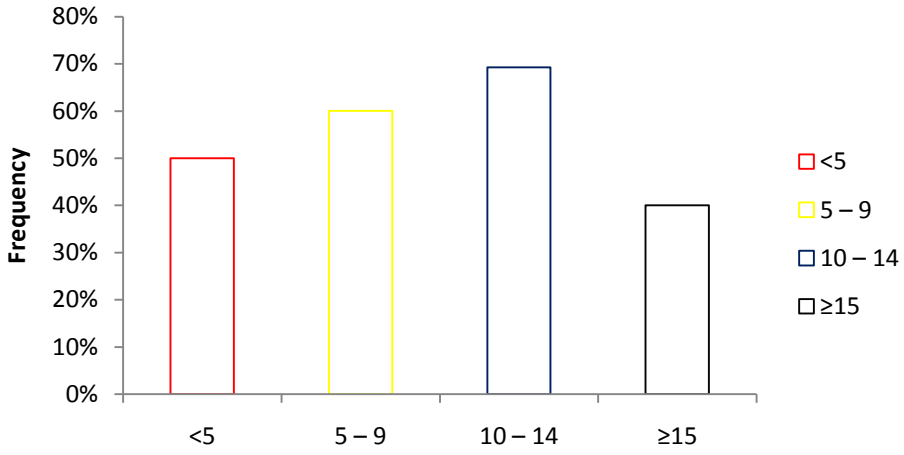

Figure 33 : Distribution of Anxiety in the Duration Groups

- The highest mean distress score for anxiety of 7.46 (SD = 3.78) was recorded for patients with a disease duration of less than 5 years, whereas patients with a duration from 5 to 9 years had the least distress score of 4.71 (SD = 3.32). **(FIG 34)**

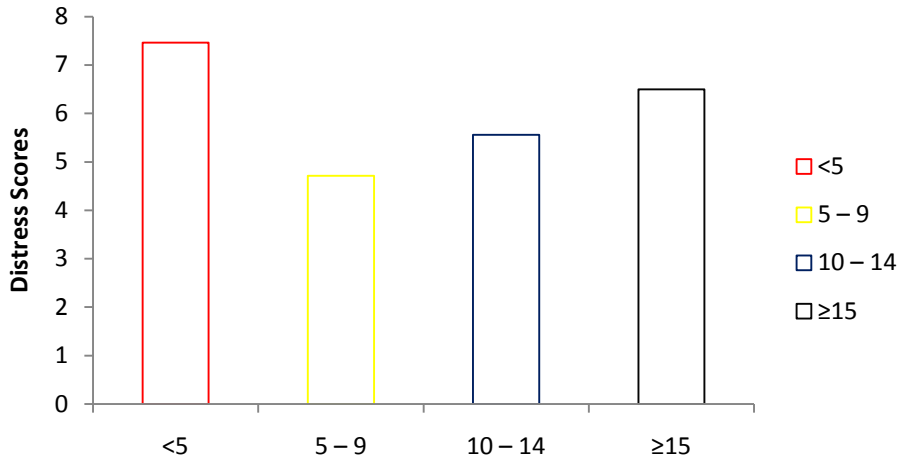

Figure 34 : Distribution of Distress Scores in the Duration Groups

2.4. Caregiver Distress

- Up to 51.11% of cases of anxiety caused some level of distress for caregivers.
- More caregivers catering for female patients (62.50%) reported distress as compared to caregivers of male patients (38.01%). **(FIG 35)**

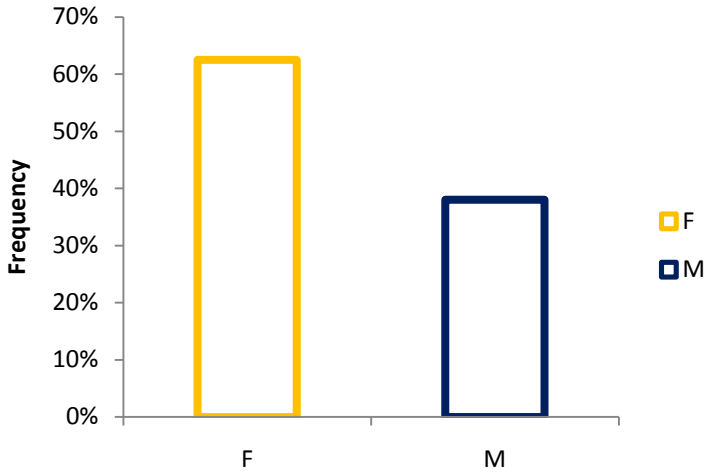

Figure 35 : Distribution of Caregiver Distress based on Gender

- The mean score was 4.13 (SD=1.25) in the caregivers catering for female patients as compared to 4.00 (SD=1.60) in male patients. **(FIG 36)**

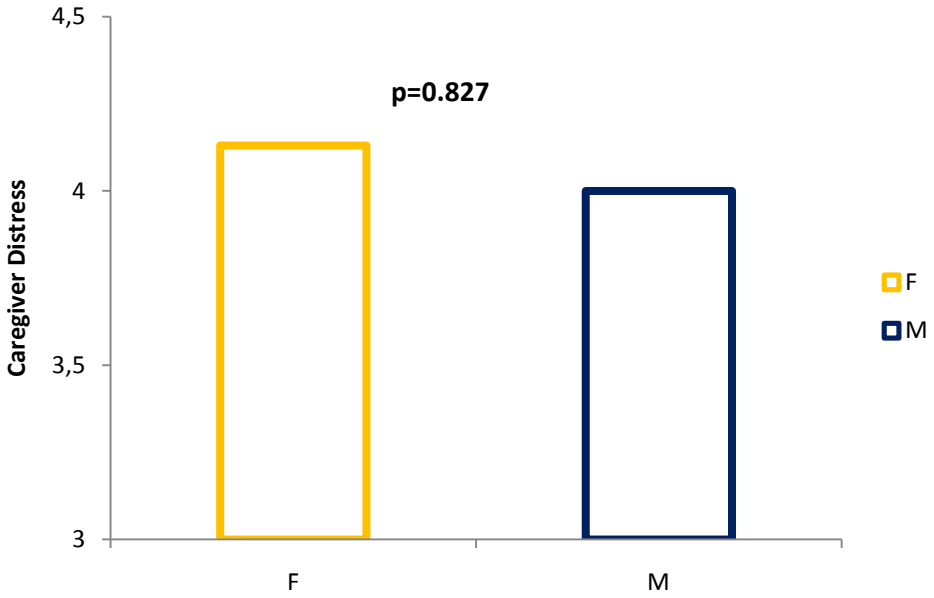

Figure 36 : Distribution of Distress Scores based on Patient Gender

- A moderate positive correlation was found between caregiver distress scores for anxiety and anxiety in patients ($r = 0.58$, $p < 0.0001$).
- The correlation between the caregiver distress scores for anxiety and anxiety in patients was stronger in male patients ($r = 0.64$, $p < 0.0001$) than in female patients ($r = 0.50$, $p = 0.001$).

2.5. Response to Treatment

- Of patients reporting anxiety, 83.64% experienced symptoms during the off state showing improvement of symptoms during the on state, while 16.36% reported symptoms during both on and off states. (FIG 37)

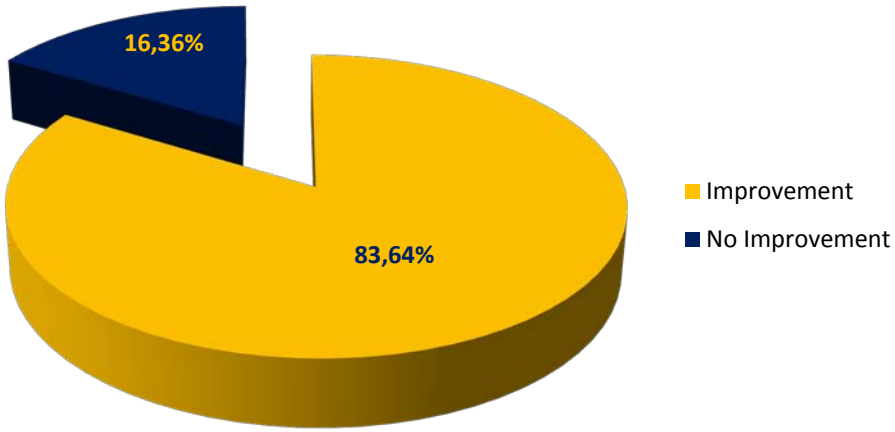

Figure 37 : Distribution of Response to L-Dopa Treatment

- There was no statistically significant difference between the male and female groups with respect to response to dopamine therapy ($\chi 2 = 0.30$, df=1, $p = 0.59$).
- Patients who responded to treatment did not differ from those without improvement of symptoms in age ($p = 0.986$), age of onset ($p = 0.868$), duration ($p = 0.2$), and L-dopa dose ($p = 0.706$).

2.6. Impact on Quality of Life

- The difference between the PDQ-8 scores of patients with anxiety and those without did not reach statistical significance (p=0.395). **(FIG 38)**

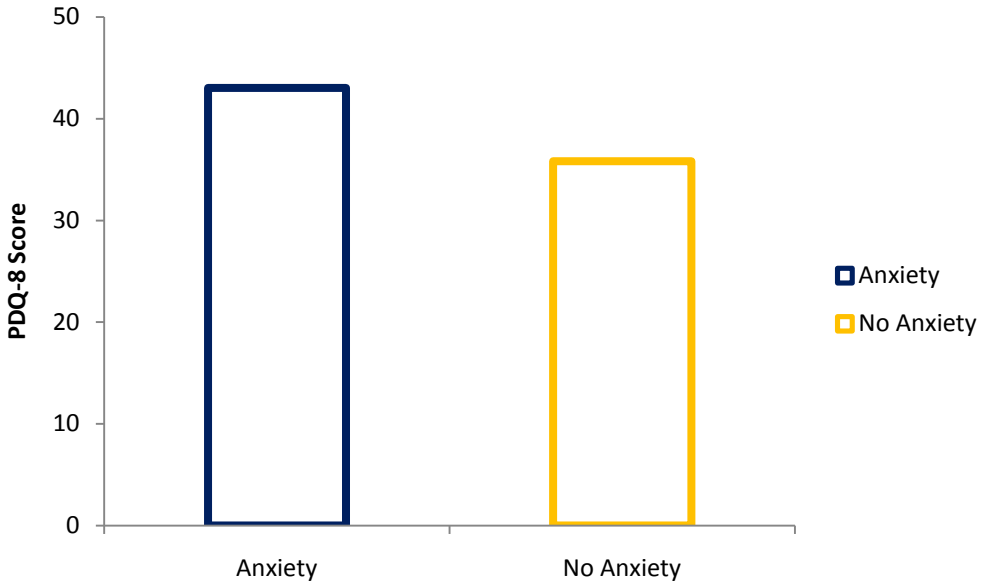

Figure 38 : Comparison of PDQ-8 Scores between Patients with and those without Anxiety

3. Psychotic symptoms

3.1. Prevalence

- Psychotic symptoms were present in 22.78% of our patients.Only 5.04% of the sample reported both delusions and hallucinations. **(FIG 39)**

a. Delusions

- Delusions were present in 13.92% of the sample. In terms of gender, 16.67% of the female patients and 11.62% of the male patients reported delusions.
- There was no statistically significant difference in terms of gender ($\chi 2 = 0.42$, $p=0.519$).

b. Hallucinations

- Hallucinations were present in 13.92% of the patient. In terms of gender, 19.44% of the female patients and 9.30% of the males patients reported hallucinations.
- There was no statistically significant difference in terms of gender ($\chi 2 = 1.68$, $p=0.195$)

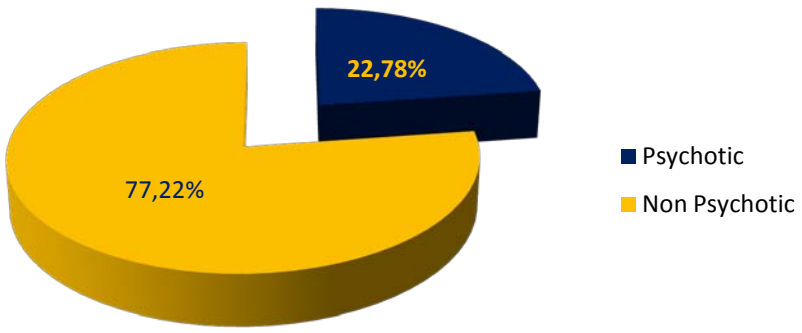

Figure 39 : Distribution of Psychosis in the Sample

3.2. Scores

a. Delusion

- In the set of patients presenting delusions, the average score was 5.27 (SD = 3.74).
- The difference in distress score across genders did not reach the level of statistical significance (p=0.807). **(FIG 40)**

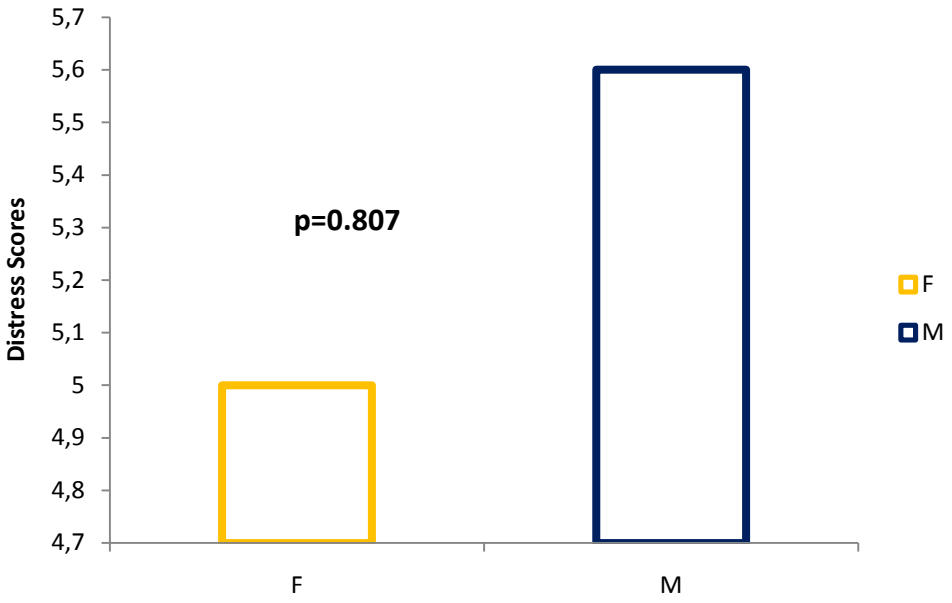

Figure 40 : Comparison of Distress Scores in Males and Females

b. Hallucination

- In the set of patients presenting hallucinations, the average score was 5.00 (SD = 2.14).
- The difference in distress score across genders did not reach the level of statistical significance (p=0.586). **(FIG 41)**

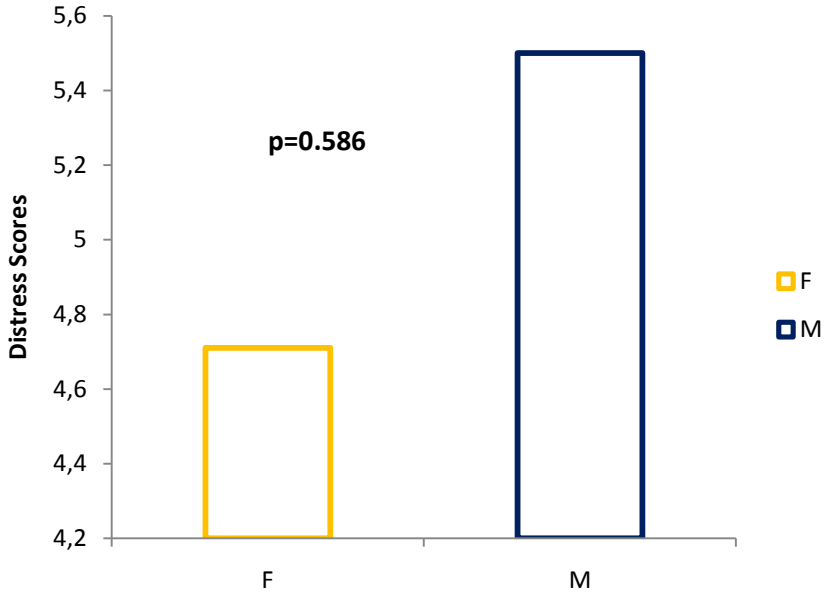

Figure 41 : Comparison of Distress Scores for Hallucinations in Males and Females

3.3. Age of Onset, Duration

- The mean age of onset of patients reporting psychotic manifestations was 51.22 years (SD=12.64).
- The mean duration of disease was 8.06 years (SD=3.95).
- No statistically significant difference was found between the group of patients with psychotic manifestation and those without in terms of age (p=0.903) and age of onset (p=0.515). **(FIG 42)**
- Patients with psychotic manifestations had a relatively longer duration with a difference approaching significance (p=0.051). **(FIG 42)**

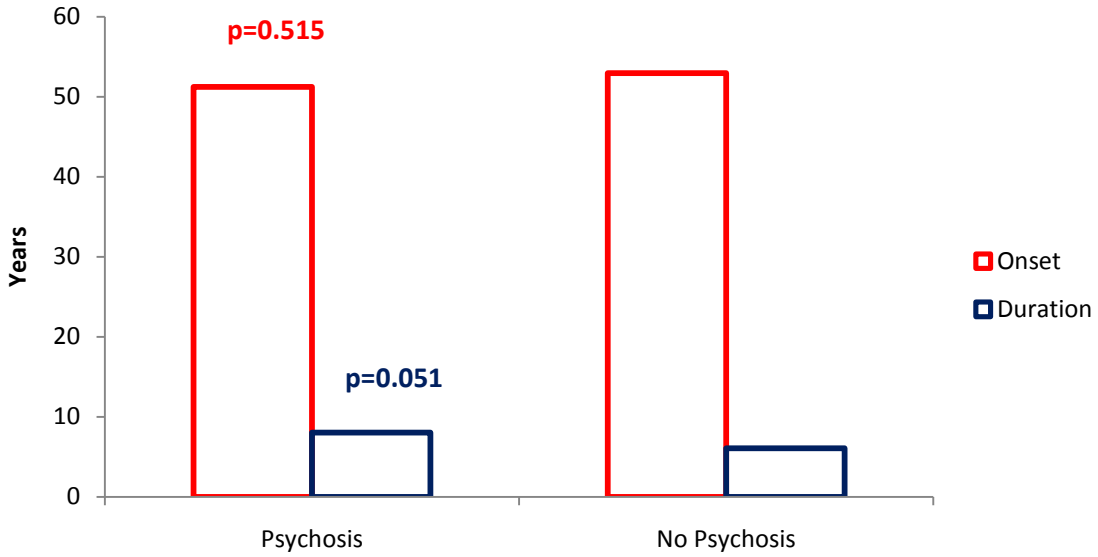

Figure 42 : Comparison of Onset and Duration in Psychotic and Non Psychotic Patients

- In terms of scores, the composite score for psychotic manifestation was highest in the 60 – 69 year age groups, and least in patients aged over 70 years. **(FIG 43)**

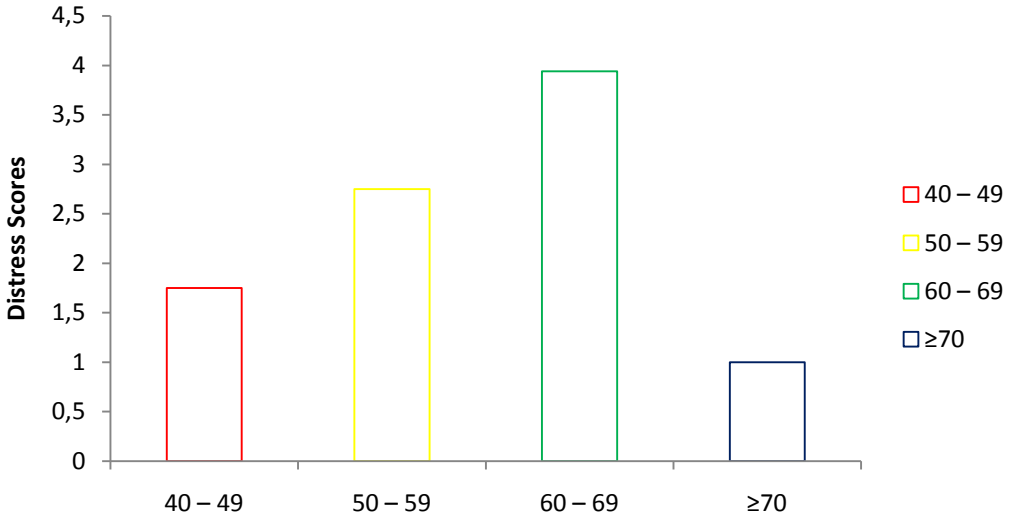

Figure 43 : Distribution of Distress Scores in Age Groups

- The highest frequency of psychotic symptoms was recorded in patients with disease duration of at least 15 years (40%), and least in patients with duration less than 5 years (15.38%). **(FIG 44)**

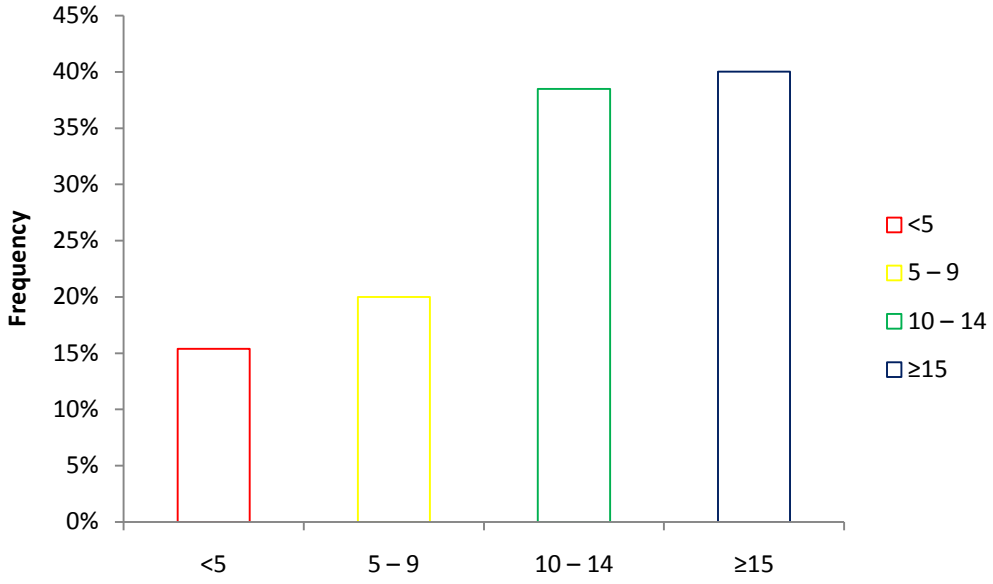

Figure 44 : Distribution of Psychosis in Duration Groups

- Patients within the 10 – 14 year disease duration group recorded the highest mean distress score of 4.7 (SD=3.42), whereas patients within the 5 – 9 year disease duration group recorded the least mean distress score of 2.43 (SD=1.34**). (FIG 45)**

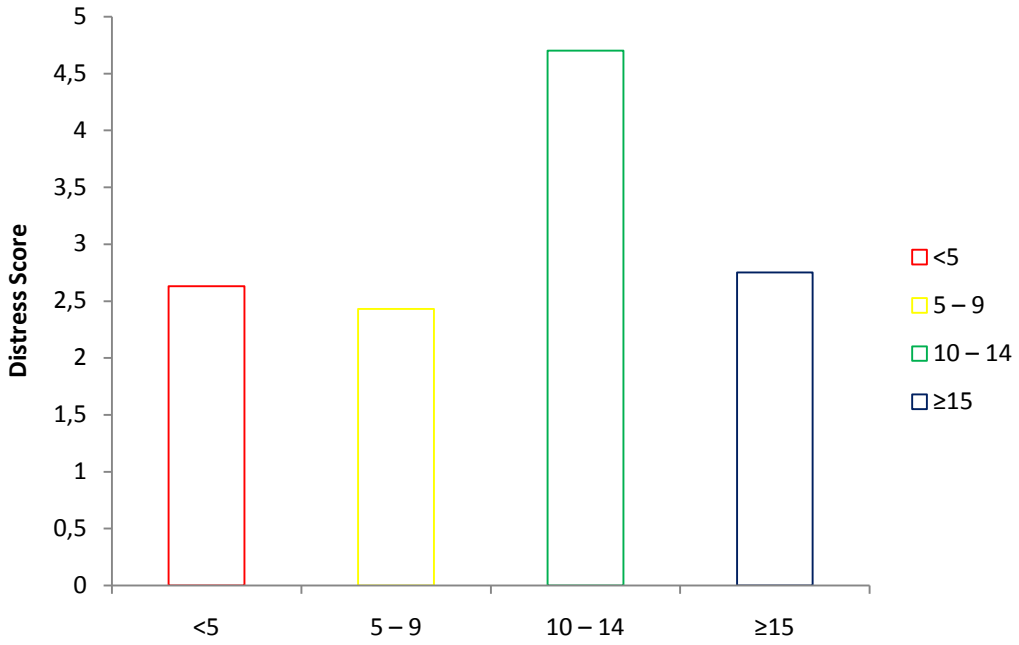

Figure 45 : Distribution of Distress Scores in Duration Groups

3.4. Caregiver Distress

- Of all the patient reporting psychotic symptoms, 50% were distressful for caregivers.
- In female patients reporting psychotic symptoms, 63.64% cause some level of distress to caregivers as against 28.57% in male patients with psychotic symptoms. (FIG 48)
- The mean caregiver distress score was 1.39 (SD=1.70).
- No statistically significant difference was observed across genders in terms of caregiver score (p=0.544). **(FIG 46)**

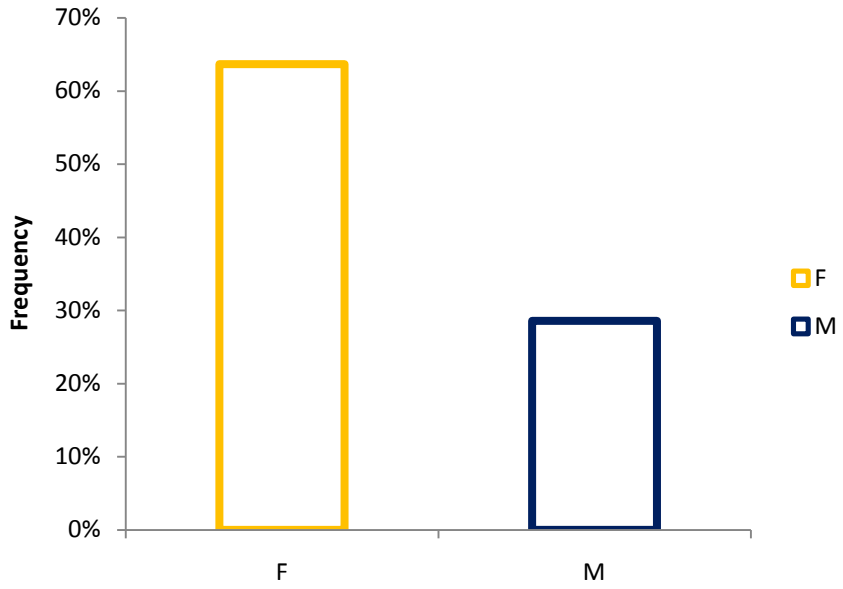

Figure 46 : Distribution Caregiver Distress based on the Gender of Patients

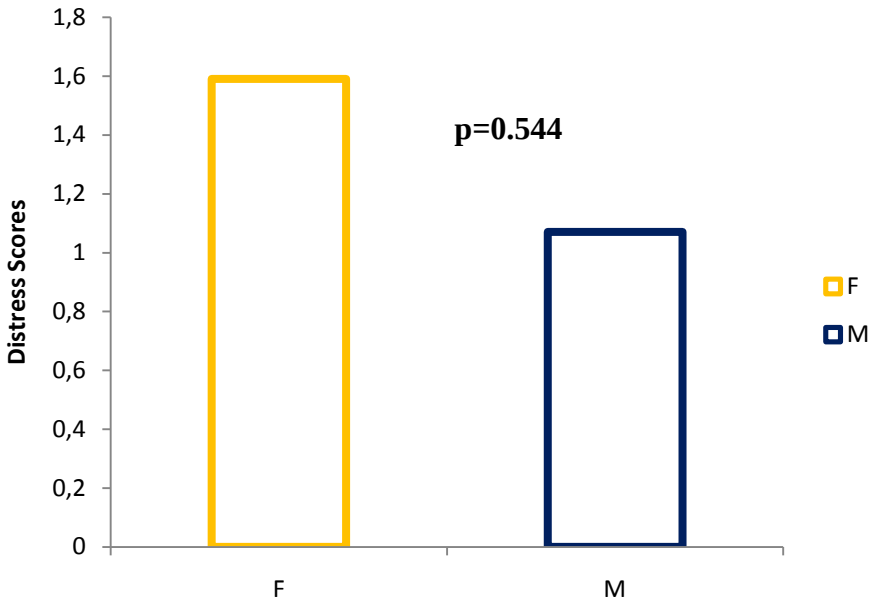

Figure 47 : Distribution of Caregiver Distress Scores based on Gender of Patients

3.5. Response to Treatment

- Of patients reporting psychotic manifestations 77.78% reported a stagnation of symptoms during the on state. The remaining 22.22% showed worsening of symptoms with L-Dopa treatment. **(FIG 48)**

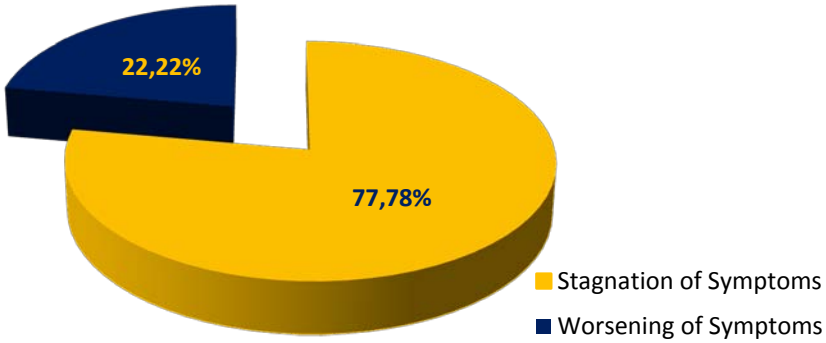

Figure 48 : Distribution of Response to Treatment

- Patients whose symptoms did not get worse with L-Dopa had a latter onset of disease (p = 0.042).
- There was no statistically significant difference between patients who reported psychotic symptoms and those who did not in terms of L-Dopa dose (p=0.745). **(FIG 49)**

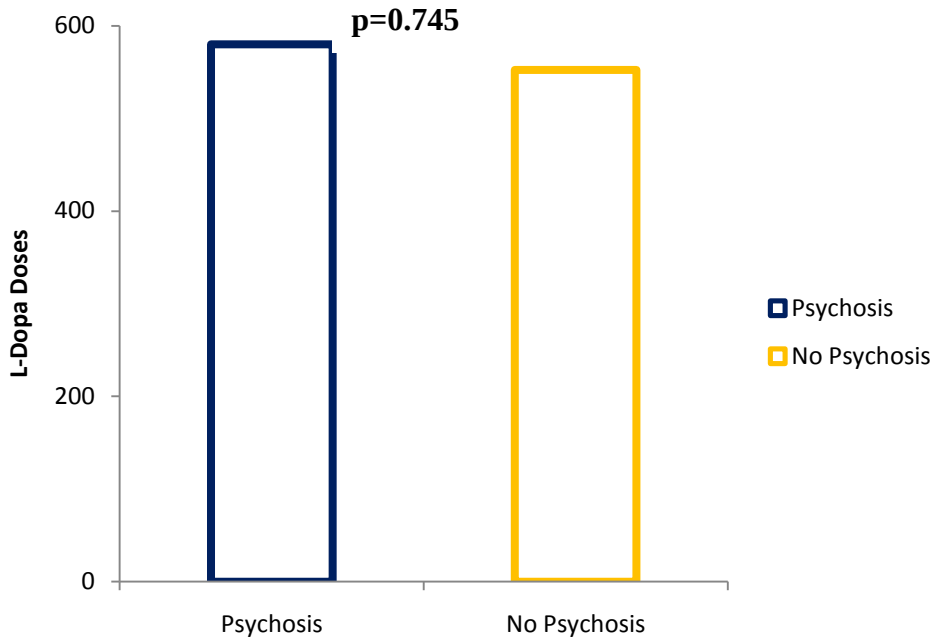

Figure 49 : Comparison of L-Dopa Dose in Psychotic and Non Psychotic Patients

3.6. Impact on Quality of Life

- The difference between the PDQ-8 scores of patients with psychosis and those without did not reach statistical significance (p=0.128). **(FIG 50)**

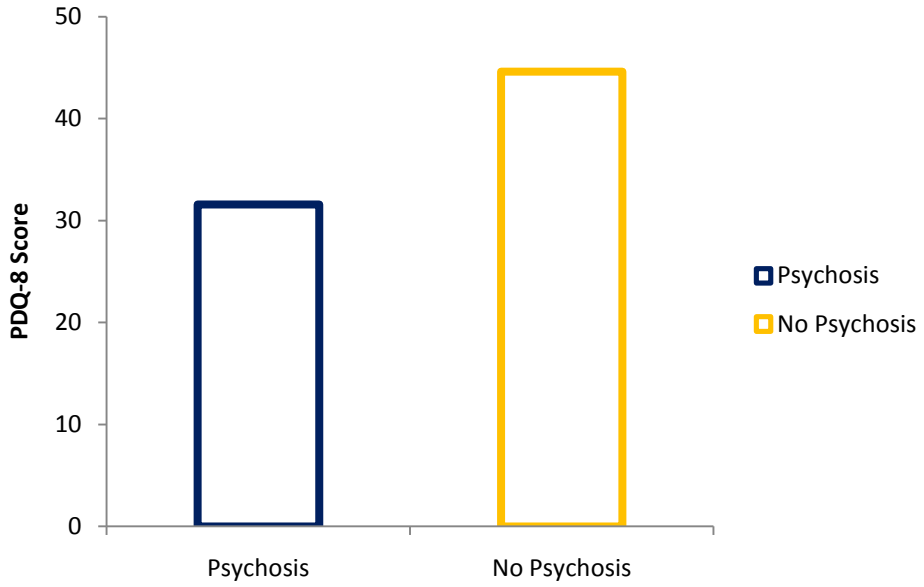

Figure 50 : Comparison of PDQ-8 Scores between Patients with and those without Psychosis

4. Apathy

4.1. Prevalence

- Apathy was present in 16.46% of our sample. **(FIG 51)**

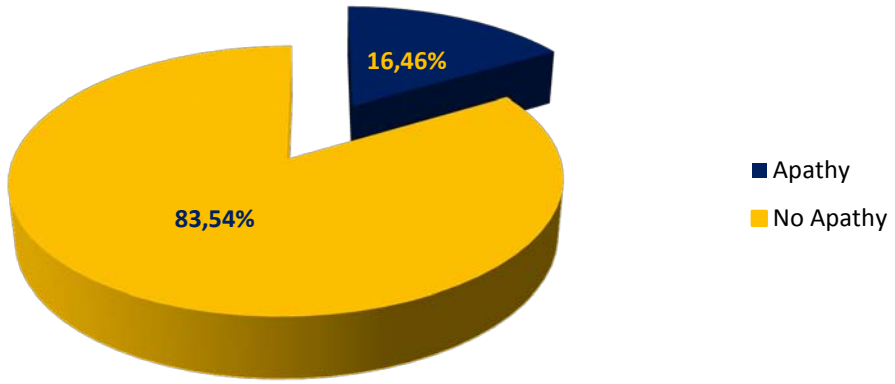

Figure 51 : Distribution of Apathy in the Sample

4.2. Score

- The average score was 3.69(SD =2.56); 3.83 (SD = 2.77) in the female group as against 3.57 (SD = 2.57) in the male group.
- The difference of distress score did not reach statistical significance across genders (p=0.863). **(FIG 52)**

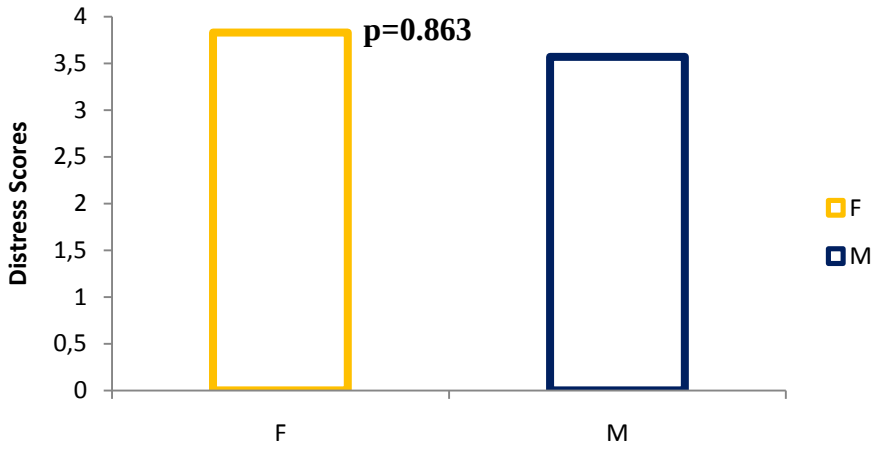

Figure 52 : Comparison of Apathy Scores across Gender

4.3. Age of Onset, Duration

- There was no statistically significant difference between patients reporting apathy and those without apathy in terms of age of onset (p=0.116) and duration (p=0.107). **(FIG 53)**

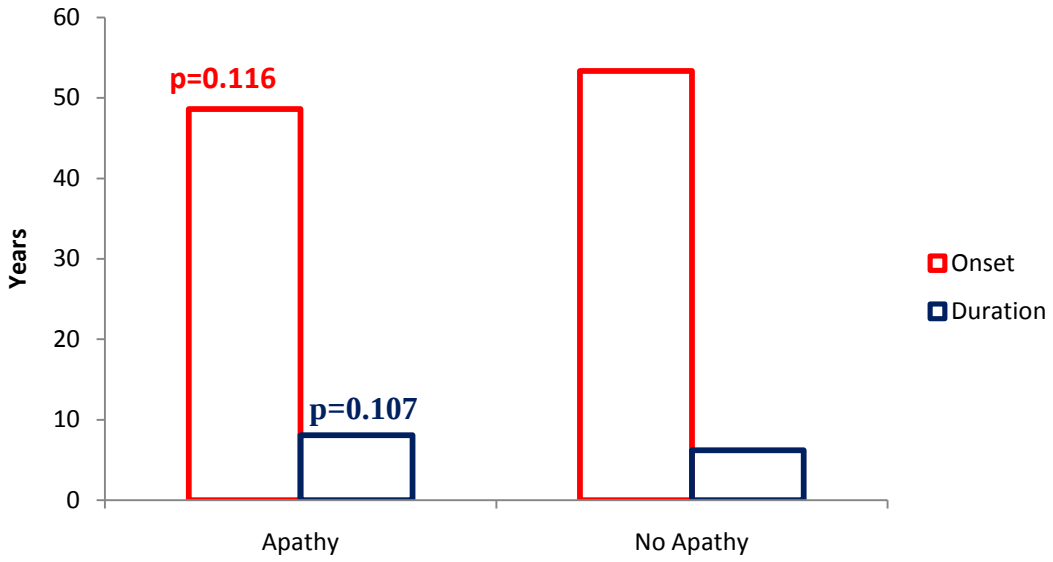

Figure 53 : Comparison of Age, Onset and Duration in Patients with and without Apathy

- Apathy was most frequent in patients with disease duration of at least 15 years (40%), and least frequent in patients with disease duration less than 5 years (11.54%).**(FIG 54)**
- The highest mean distress score of 6.00 (SD=4.36)was recorded in patients within the 10 – 14 year duration group, whereas the lowest mean distress score of 2.33 (SD=1.53) was recorded in patients with duration less than 5 years.**(FIG 55)**

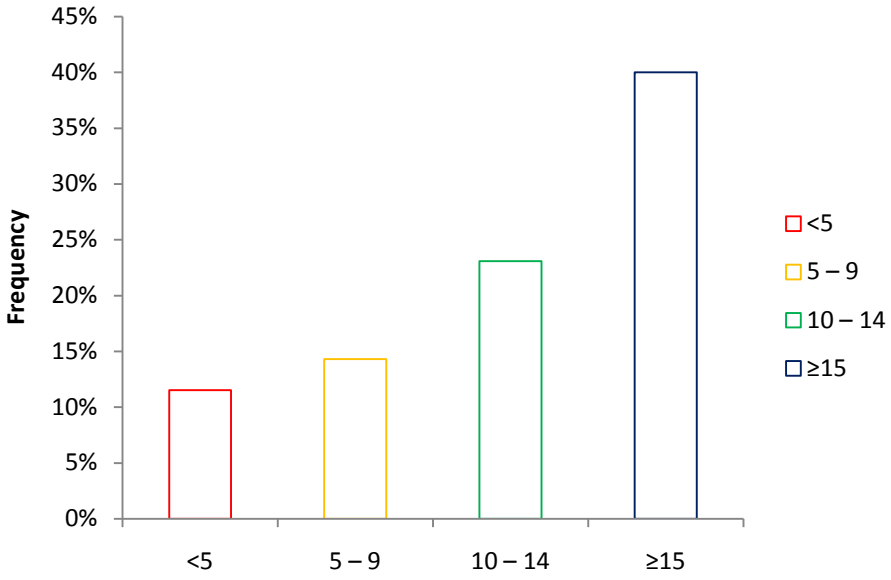

Figure 54 : Distribution of Apathy in the Duration Groups

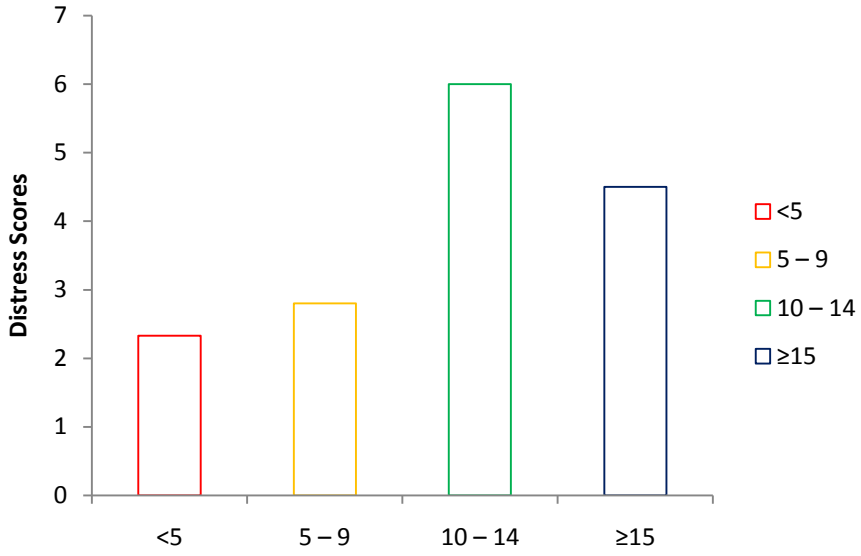

Figure 55 : Distribution of Apathy Scores in Duration Groups

4.4. Caregiver Distress

- Up to 30.77% of cases of apathy caused some level of distress for caregivers.
- In terms of gender, caregivers of 33.33% of female patients with apathy reported some level of distress, whereas, caregivers of 28.57% of male patients with apathy reported some level of distress. **(FIG 56)**

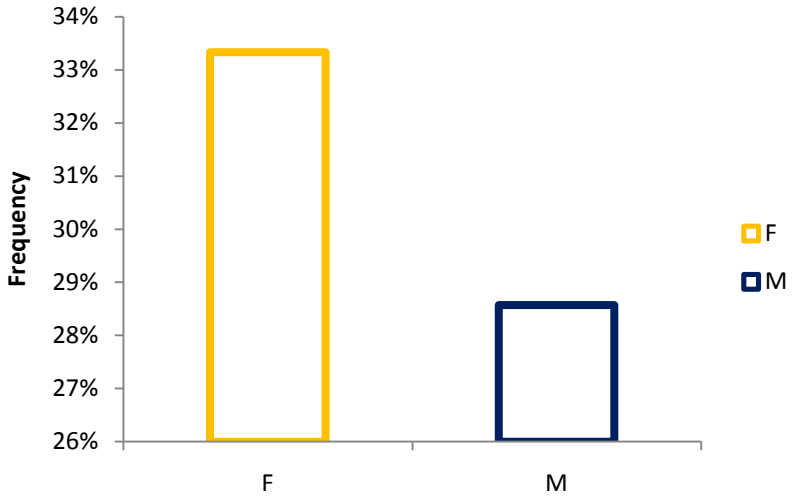

Figure 56 : Distribution of Caregiver Distress based on Gender

4.5. Response to Treatment

- Of patients reporting apathy, 63.16% experienced symptoms during the off state showing improvement of symptoms during the on state, while 36.84% reported symptoms during both on and off states. **(FIG 57)**

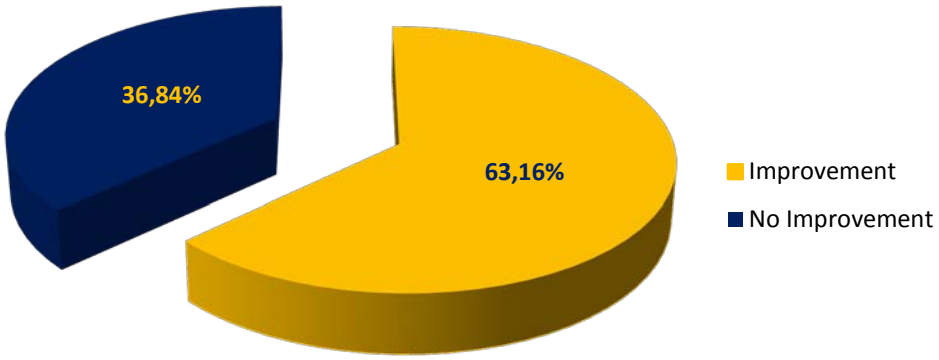

Figure 57 : Distribution of Response to Treatment

- There was no statistically significant difference between the male and female groups for apathy fluctuation response to dopamine therapy ($\chi 2=2.42$, df=1, p = 0.12).
- Patients who responded to treatment did not differ from those without improvement of symptoms in age (p= 0.467), age of onset (p= 0.543), duration (p= 0.703).
- Patients who responded to treatment received relatively lower doses of L-dopa of 510mg (SD=279.30). The difference approached statistical significance (p= 0.073).

4.6. Impact on Quality of Life

- The difference between the PDQ-8 scores of patients with apathy and those without did not reach statistical significance (p=0.153). **(FIG 58)**

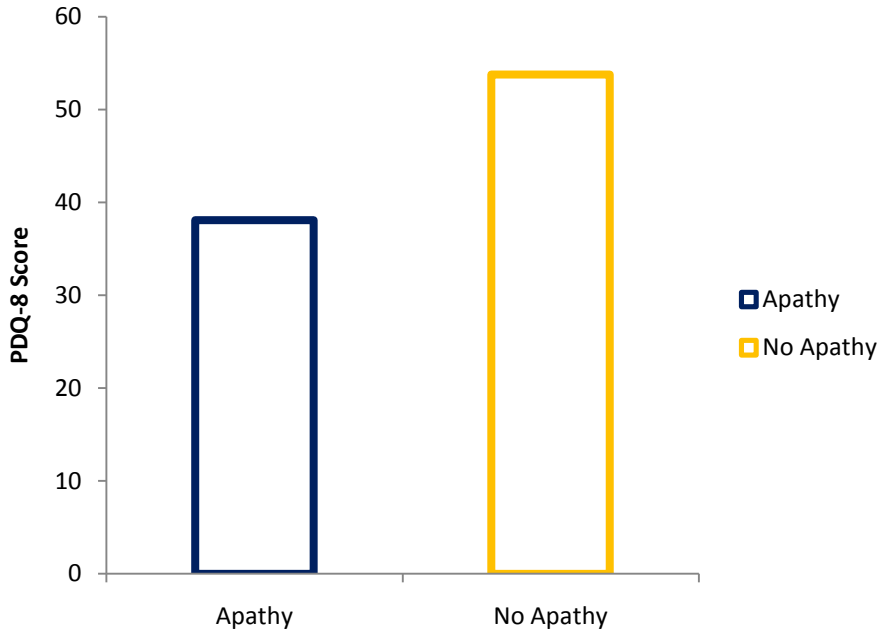

Figure 58 : Comparison of PDQ-8 Scores between Patients with and those without Apathy

5. Behavioral Symptoms

5.1. Prevalence

- Impulse control issues were present in 22.78% of the general sample. **(FIG 59)**

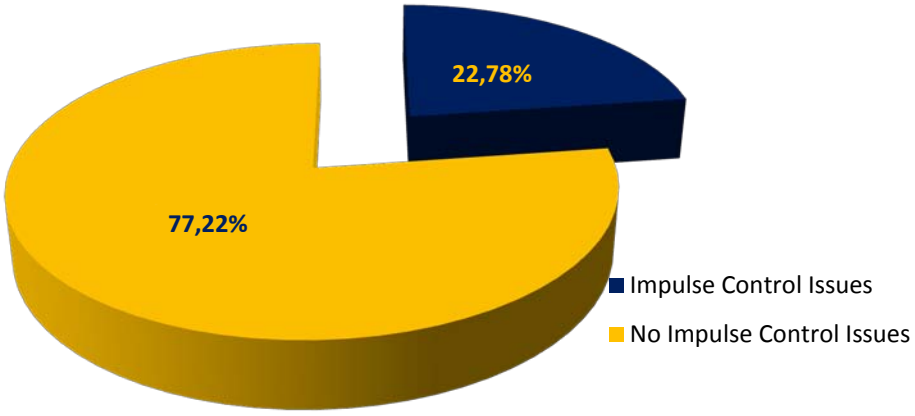

Figure 59 : Distribution of Impulse Control Issues in our Sample

- Dopamine Dysregulation Syndrome was found in 17.24% of our patients. **(FIG60)**

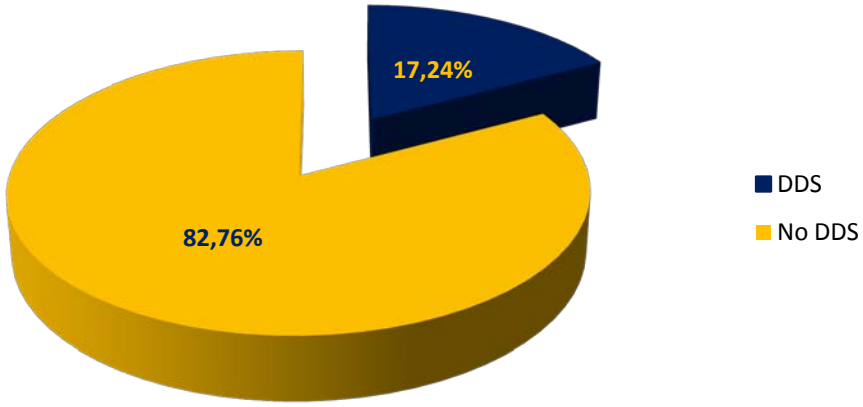

Figure 60: Distribution of Dopamine Dysregulation Syndrome in our Sample

5.2. Age of Onset, Duration

- Patients with behavioral issues did not differ from those without in terms of onset or duration.
- Patients with was most frequent in patients with a disease duration of at least 15 years (80%). **(FIG 61)**

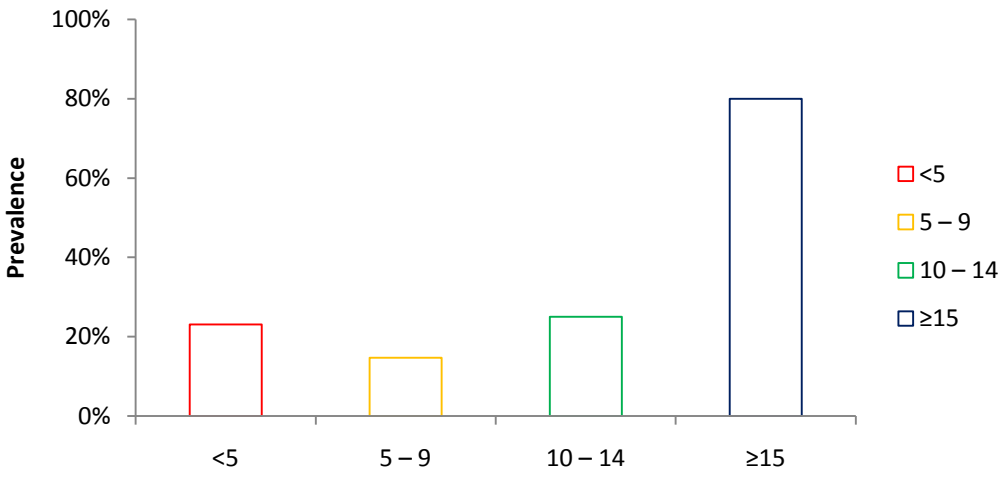

Figure 61 : Distribution of Impulse Control Issues across Duration Groups

5.3. Response to Treatment

- Of patients reporting impulse control symptoms, 16.67% experienced a stagnation of symptoms during the on state, while 83.33% reported a worsening of symptoms. **(FIG 62)**

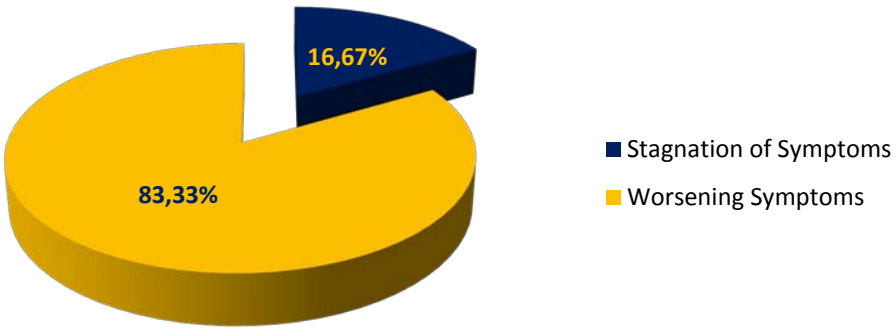

Figure 62 : Distribution of Response to Treatment

5.4. Impact on Quality of Life

- The difference between the PDQ-8 scores of patients with apathy and those without did not reach statistical significance (p = 0.593). (**FIG 63**)

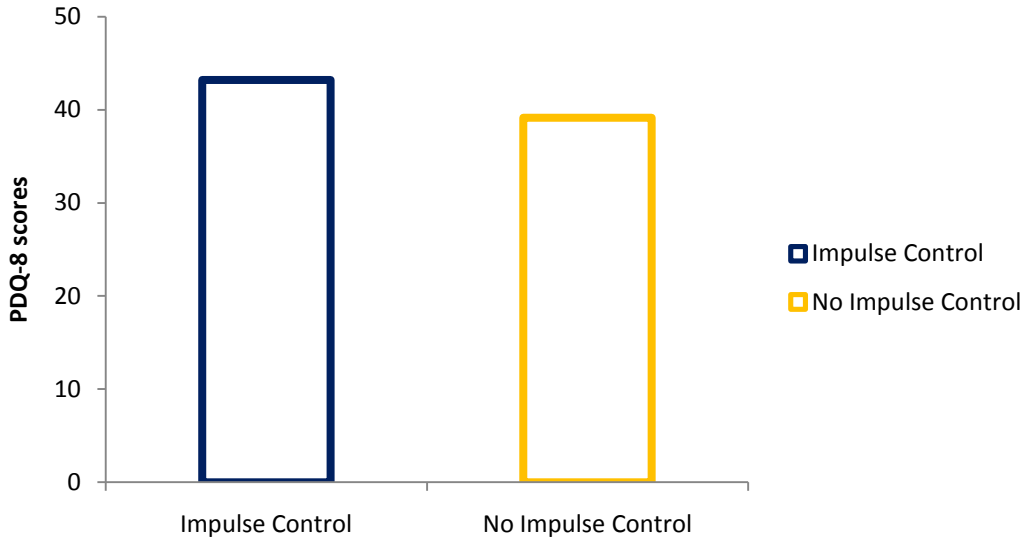

Figure 63: Comparison of PDQ-8 Scores between Patients with and those without Impulse Control Issues

DISCUSSION

I. General Findings

1. Gender

Parkinson's disease showed a slight male predominance in our sample. Male patients represented a little over 54% of the study cohort. The sex ratio was 1.19.

Our findings are in line with most of the literature. Parkinson's disease is thought of as being a disease of predominantly male patients [43 – 45]. Several studies have found similar sex ratios as ours, and sometimes, even higher ratios [46, 47]. In fact, a study conducted in the same population of Parkinson's disease patients in our unit found a much higher ratio of 1.42 [48].

Several explanations could be given for this male predominance. First, the "estrogen hypothesis" posits the neuroprotective role of estrogens in females [49 – 51]. Secondly, the "X-chromosome hypothesis" has been put forward based on recent genetic linkage studies that have revealed the presence of a Parkinson's disease susceptibility gene on the X-chromosome [52]. Thirdly, the "male lifestyle hypothesis" suggests that head trauma and toxic exposure, both risk factors of Parkinson's disease, and incidentally, more frequent in males, could explain the male predominance [41].

Also, it is known that males, in general, have greater access to healthcare than females [53]. Therefore, based on our ascertainment cohort, what Dejan et al. term a "hospital-clinical population" [54], we might have inadvertent introduced a bias into our selection process. This fact is however counterpointed by the finding that females tend to participate more readily in research [55].

Interestingly, it has been shown in the literature that depending on which method of patient selection is used, we could either end up with no difference in prevalence of Parkinson's disease with respect to gender [56, 57] or, even, a female predominance [58]. However, it must be noted that the majority of studies point to a male predominance. **(TABLE II)**

TABLE II : Comparison of sex ratios in our study with other series

Study	Place	Year	Sex ratio
Wender et al. [59]	Poland	1989	1.30
Wang et al. [60]	China	1991	1.24
Granieri et al. [61]	Italy	1991	0.88
Mayeux et al. [62]	USA	1991	1.51
Kuopio et al. [46]	Finland	1999	1.95
Vines et al. [47]	Spain	1999	2.06
Bower et al. [63]	USA	1999	1.48
Our Study	Morocco (Marrakech)	2019	1.19

2. Place of Residence

Nearly 65% of our patients hail from rural areas. Rural areas are in general associated with lower socio-economic status and limited access to healthcare. These especially are areas more prone to the "male lifestyle" with greater exposure to toxic substances seeing as these are essentially agricultural communities. As such, some association indeed exists between Parkinson's disease and the place of residence of patients. Several studies in the literatures point to living in a rural area as possible risk factor of Parkinson's disease. Furthermore, associations have been found between exposure to pesticides and herbicides in agricultural areas, and the drinking of non potable water as risk factors of Parkinson's disease[64]. In fact, Gorell et al. pointed out that the association between farming in rural areas, and the development of Parkinson's disease could not be explained by exposure to pesticides only[65]. This suggests that living in a rural area in and of itself might be a risk factor for Parkinson's disease. It is important to make the precision that the association is not with previous living but with present residence in a rural area[66].

We point out, however, that while our study investigated the general case of rural/urban dwelling, we did not specifically investigate the use of non potable water, exposure to pesticides and herbicides, and occupation.

It is furthermore worth-noting that while we can conveniently explain the predominant rural residence in our sample in terms of risk factors, another possible explanation for our finding

is the bias introduced in using a "hospital-clinical population"[54] in our study. That is, we might simply be dealing with patients with limited means from the rural areas while the patients with greater access and larger means seek medical attention in the private setting.

3. Health Insurrance

Only some 15% of our patients had health insurance. The added fact of rural predominance of our sample reveals the low level of socio-economic status of our patients. This reality limits patients' access to healthcare and influences the management of the disease seeing as these patients would have to pay for their medication, and would have to continue medication for life.

4. Patient History

Some 44% of our sample had a history of some medical condition or toxic exposure. High blood pressure (29%) and type 2 diabetes (13%) were the most frequent co-morbid conditions. This finding is in line with the literature. Santos et al. in a longitudinal study also found that hypertension and diabetes were the most frequent co-morbidities in Parkinson's disease [67]. According to Mithal et al., hypertension, hyperlipidemia and diabetes were the most frequent co-morbidities[68]. **(TABLE III)**

Several other studies have found various associations between Parkinson's disease and diabetes[69 – 72]. This has led to hypotheses tying both diseases at the pathophysiological level. In fact, several other studies have pointed to the role diabetes plays in other neurodegenerative diseases like Alzheimer's disease [73] and Amyotrophic Lateral Sclerosis [74].

Parkinson's disease is a disease of the elderly. It is therefore not bewildering that it should be associated with other diseases of old age. Co-morbid conditions therefore could be present simply due to an ageing biology. Research, however, suggests that Parkinson's disease and diabetes, as well as depression, share common inflammatory pathways [75 – 78]. This has led to clinical trials testing new biomarkers and the efficacy of diabetes medication in Parkinson's disease [79– 89].

TABLE III : Comparison of most frequent Co-morbidities in our study with other series

Study	Place	Year	Hypertension	Hyperlipedemia	Diabetes
Malek et al. [90]	UK	2016	30%	-	7%
Mithal et al. [68]	USA	2017	37.8%	21.2%	19.1%
Santos et al. [67]	Spain	2017	40+%	-	15%
Our Series	Morocco (Marrakech)	2019	29%	-	13%

5. Age, Onset, Duration

The mean age of our sample was 59 years. This is in line with the literature seeing as Parkinson's disease is an appanage of old age, usually patients older than 50 years[23]. Our finding closely mirrors results in an Italian study by Accolla et al. who found a mean age of 59.8 years[91]. The mean age in our sample was however relatively smaller than in several other studies. Yoritaka et al., for example, found 68.5 years in a study conducted in a Japanese population of Parkinson's disease patients[92]. Our patients therefore are relatively a younger sample.

The mean age of onset in our sample was 52.6 years. Thus our patients present symptoms much later than the Accolla patients (45.7 years) but much earlier than the Yoritaka patients (62.0 years).The mean age of our sample practically lies midway between the Accolla and Yoritaka samples. Our patients are therefore of unbiased age at onset of disease.

To be clear, over a third (35%) of our sample had an age at onset below 50 years, and would therefore qualify as early age of onset Parkinson's disease. Our findings seem to be higher than findings in the literature. Pagano et al., in a single-center prospective study, found an onset before 50 years in 13.7% of their sample[93]. In a similar study, Diamond et al. found a prevalence of 24.0% in patients with onset before 50 years[94]. **(TABLE IV)**

TABLE IV : Comparison of Prevalence of Parkinson's disease before 50 years in our study with other series

Study	Place	Year	Prevalence
Teravainen et al. [95]	Canada	1986	2.34%
Diamond et al. [94]	USA	1989	24.07%
Pagano et al. [93]	UK	2016	13.74%
Our Study	Morocco (Marrakech)	2019	35%

The mean duration of disease at the time of study was found to be 6.5 years in our sample. This resembles findings in the Yoritaka sample (6.4 years) but is far smaller than the Accolla sample (14.8 years). Our patients are therefore of relative recent diagnosis. **(TABLE V)**

TABLE V : Comparison of Age and Duration in our Patients with other Studies

Study	Place	Year	Age, yrs	Onset, yrs	Duration, yrs
Zappia et al. [96]	Italy	2002	66.0	-	6.5
Acolla et al. [91]	Italy	2007	59.8	45.7	14.8
Clark et al. [97]	USA	2008	60.2	-	7.3
Yoritaka et al. [92]	Japan	2009	68.5	62.0	6.4
Our study	Morocco (Marrakech)	2019	59.0	52.6	6.5

Furthermore, we found a slightly younger mean age of onset in females (51.1 years) than in males (53.8 years). This means, on average, females would present symptoms some 2.7 years before males.This seems to go contrary to what we would expect given the "estrogen hypothesis". If estrogen protects females then they should have Parkinson's disease less frequently, and if they do, it should occur much later than males. Our study found a male predominance.

Haaxma et al. [98] found, like in other studies[99], that females tended to be a little much older than males at the time of diagnosis. A correlation was found between number of children, age of menopause and duration of fertile life.

Given our context, the neuroprotective role of estrogen should confer a latter age of onset to females. To explain our finding, we suggest that, it is not a matter of estrogen protection but that of some protective lifestyle in males – caffeine and nicotine. Though these factors were not investigated in our sample, it is an undeniable fact that males in our context are avid consumers of caffeine and nicotine. This "caffeine-nicotine hypothesis" [41] could be the male surrogate of the "estrogen hypothesis" in our context.

It is worth-noting, however, that the protective role of caffeine and nicotine have been inconsistently found in different studies and need further investigation [100]. That aside, it is also true that there is no monopoly in the literature of a later onset of Parkinson's disease in females [101 – 3].

All in all, differences observed between our sample and samples from other studies could be due to different genetic substrates and environmental exposure, as well as the peculiar lifestyles of each sample.

6. Clinical Symptoms

Neuropsychiatric symptoms were highly prevalent among our patients with up to 95% of patients reporting symptoms. Our findings are similar to findings made by Aarsland et al. who found a prevalence of 90% for neuropsychiatric manifestations in Parkinson's disease [104]. Several other studies have shown that neuropsychiatric manifestation are highly prevalent in Parkinson's disease, and could even predate motor symptoms [105]. **(TABLE VI)**

TABLE VI : Prevalence of Neuropsychiatric Symptoms in our Sample compared to other Series

Study	Place	Year	Prevalence
Aarsland et al. [106]	Norway	1999	61%
Aarsland et al. [104]	Norway	2007	90%
McKinlay et al. [107]	New Zealand	2008	80%
Our Study	Morocco (Marrakech)	2019	95%

The most frequent symptoms in our study were depression (77%), irritability (67%), anxiety (57%) and sleep disorders (52%). Depression has been found to be the most frequent neuropsychiatric symptom in several other studies[108]. Aarsland et al. [104] reported a frequency of 57.5% whereas McKinlay et al. [107] reported a frequency of 42.2%. Apathy was found to be one of the least occurring symptoms in our sample (16%). However, McKinlay et al. and Aarsland et al. reported higher frequencies of 27.9% and 54.3% respectively.

Symptoms were also highly associative with up to 91% of patients reporting at least two diagnoses simultaneously. On average, a patient reported approximately four different diagnoses simultaneously. Females reported more symptoms than males on average.

Symptoms were also highly distressful for patients. In up to 85% of our patients, the distress was moderate to severe in at least one of the neuropsychiatric manifestations. Our finding is much higher than that found in the Norwegian population with only 64% of patients reporting moderate to severe distress in at least one of the neuropsychiatric manifestations [104]. Furthermore, the mean total score in our sample (22.57) was significantly much higher than in the Norwegian Parkinson's disease population (12.9). Our study found that females reported a significantly greater level of distress than males.

A similar pattern was observed with respect to quality of life with females reporting worse outcomes compared to males (52.8 vs 34.8). Our patients reported worse quality of life outcomes compared to other populations [109 - 111]. **(TABLE VII)** This could be due to an insufficient management of our patients especially given the low socio-economic level of our patients, and limited access to healthcare.

TABLE VII : Comparison of PDQ-8 Scores in our Sample with other Series

Study	Place	Year	
Wood et al. [109]	UK	2002	15.42
Katsarou et al. [110]	Greece	2003	25.86
Jenkinson et al. [111]	USA	2006	30.72*
Jenkinson et al. [111]	Canada	2006	31.40*
Jenkinson et al. [111]	Italy	2006	39.07*
Jenkinson et al. [111]	Spain	2006	26.64*
Jenkinson et al. [111]	Japan	2006	27.16*
Our Study	Morocco (Marrakech)	2019	43.11

*Multicenter global study

In our study, depression was the best predictor of quality of life outcomes. This finding is similar to findings in the literature[112,3]. Aggressivity was the only other symptom which approached significance as a predictor of quality of life outcomes in our patients. The non significant levels of the other symptoms could be explained by an insufficient sample size.

An observation worthy of note is the general trend in which females reported more symptoms than males. This trend has been observed in the general population and is not a

Parkinson-specific trait. Scott et al. attributed these gender-based differences in mood disorders to "differences in social acceptance of communicating emotionality."[114]

This points to a major role of gender, not only as a biological definition, but also as a socio-cultural reality which is pivotal in the phenomenology of these neuropsychiatric manifestations. This reality goes beyond the self-perception of patients. It does also influence the perception of patients by their caregivers. We found for example, that caregiver distress score for depression was better correlated to the level of depression of the patients for males than for females. As such, caregiver distress was better explained by the distress of the patients in males than in females. This points to the role of the psychosocial context not only in the etiology, but also, in the management of these symptoms.

Finally, it should be pointed out that the literature on Parkinson's disease is rife with variations.

An interesting point to consider in this overview is the fact that there exists a grand variability of findings in the literature on Parkinson's disease. There are no converging rates for prevalence, and several associations are inconsistently found, or contrary findings are made. To explain this, we point out that (1)Variations in study population, (2) Diagnostic tools and methodologies, and (3) Definition of symptoms may have major roles to play in the disparity[115 – 8].

II. Specific Findings

1. Depression in our Patients

Depression was the most frequent neuropsychiatric manifestation in our study. While this is true of depression in Parkinson's disease in the literature, our patients seem to have a higher prevalence compared with other populations. **(TABLE VIII)** This might be due to more advanced disease stages in our patients. Alternatively, our finding could be an indicator of poorer management of patients, in part due to their socio-economic status, the insufficient access to health, and an inadequate psychosocial support.

TABLE VIII : Prevalence of Depression in our Samplecompared with other Series

Study	Year	Prevalence
Cummings et al. [119]	1992	43%
Chen et al. [120]	2007	18.5%
Reijnders et al. [121]	2008	35%
Our Study	2019	77.2%

Depression is a source of considerable distress for patients and their caregivers[104]. In our patients, it was associated with worse quality of life outcomes. This is in line with the literature which places depression as the most important indicator of quality of life[113, 116]. Depression has beenshow in several studies to be associated withworsening of motor symptoms, cognitive impairment, reduced quality of life, increased disability, increased psychiatric and medical co-morbidity, and greater health-care utilization[122, 123].

In addition, we found in our study that patients likely to report depression were (1) females, (2) patients with younger age of onset, (3) patients with longer duration of disease ≥10 years, (4) cognitively impaired patients, especially delusional patients, (5) patients receiving higher doses of levodopa.

Our findings bear resonance to the literature with general risk factors for depression in Parkinson's disease given to include, longer duration of the disease[124], predominance of right-sided motor symptoms[125], presence of other neuropsychiatric symptoms[126 – 7],

presence of sleep disorders[128 – 9], higher daily doses of levodopa[130], younger age[130], and female gender[131]. **(TABLE IX)**

TABLE IX : Comparison of Associations Found with Depression in Our Study and Other Studies

Associations and Possible Risk Factors	Our Study, 2019	Other Studies
Right-side symptoms	No	Starstein et al., 1990[125]
Cognitively impaired	Yes	Tandberg et al., 1996[132]
Younger age of onset	Yes	Tandbeg et al., 1997[130]
Higher levodopa dose	Yes	Tandbeg et al., 1997[130]
Sleep disorder	Yes	Tandberg et al., 1998[128]
Female	Yes	Rojo et al., 2003[131]
Number of symptoms	Yes	Marsh et al., 2004[126]
Longer duration	Yes	Wichowicz et al., 2006[124]

For caregivers, depression was the most frequent cause of distress with nearly 48% of caregivers catering for depressed patients reporting some level of distress.

Depression responded well to L-Dopa treatment in our patients. This is highly suggestive of the overlapping of neurobiological mechanisms between depression and motor symptoms[133 – 4].

2. Anxiety in our Patients

Anxiety was one of the most frequent neuropsychiatric symptoms experienced by our patients. Our findings are in line with the literature in terms of the ranking of anxiety as second most common affective disorder in Parkinson's disease after depression [106, 135].

Our finding of a high prevalence of anxiety is consistent with the literature though a prevalence of 57% in our sample is a little higher than findings in other studies[136 – 7]. In fact, anxiety is known to be much less frequent in the geriatric population as compared to younger age groups[138 – 9]. **(TABLE X)**

Furthermore, anxiety in Parkinson's disease exceeds, by far, anxiety in any other medical illness of comparable disability[140].

This exceedingly high prevalence of anxiety in Parkinson's disease gives something of an "epidemiological credence" to the hypothesis that anxiety is of overlapping neurobiological basis as Parkinson's disease[141 – 2], rather than a mere reactionary phenomenon.

TABLE X : Prevalence of Anxiety in Parkinson's Disease as Compared with the General Population

Study	Year	General Population	Parkinson's Disease Patients
Regier et al. [138]	1988	7.3%	-
Bland et al. [139]	1988	6.5%	-
Pontone et al. [143]	2009	-	49%
Negres-Pages et al. [140]	2010	-	51%
Our Study	2019	-	57%

Anxiety was an important source of distress for our patients and their caregivers. Our study found no association between anxiety and quality of life. Several studies have however found some association[144]. Our results might be due to an insufficient sample size.

The risk factors for anxiety as found in the literature areyoung-onset Parkinson's disease[143], severity of Parkinson's disease and symptom clustering[145], depressive symptoms, worst sleep quality, being nonwhite, female gender, and younger age[146 – 8]. **(TABLE XI)**

TABLE XI : Comparison of Associations with Anxiety in Our Study and Other Studies

Study	Mezna et al.[149]	Babson et al.[150]	Negre-Pages et al.[147]	Dissanayaka et al.[145]	Dissanayaka et al.[151]	Our Study
Year	1993	2008	2010	2010	2015	2019
Female	-	-	Yes	-	Yes	Yes
Depression	Yes	-	-	-	Yes	Yes
Severe Outcomes on NPI	No	-	-	-	-	Yes
Duration	-	-	-	Yes	-	Yes
Sleep Disorders	-	Yes	-	-	-	Yes
Younger Age	-	-	Yes	-	Yes	Yes
Younger Onset	-	-	-	-	Yes	No
LevoDose	No	-	-	No	No	No

3. Psychotic Symptoms in our Patients

Psychotic manifestations were among the least frequent symptoms in our sample. All together, 23% of our patients reported psychotic manifestations: 14% of the sample presented delusions, and 14% as well presented hallucinations. Only 5% reported both delusions and hallucinations.

Our finding of a low frequency is similar to findings made by McKinlay et al. who found a prevalence of delusions and hallucinations to be 4% and 9% respectively[107]. Conversely, Aarsland et al. found a higher prevalence of 25% and 44% respectively for delusions and hallucinations in their study[104]. The differences in our findings could be explained by differences in the sample characteristics: the Aarsland sample was much older than our sample (72.6 years), and they had had the disease for a longer period (10 years). **(TABLE XII)**

TABLE XII : Comparison of Prevalence of Hallucinations in Our Patients with Other Studies

Study	Place	Year	Prevalence
Aarsland et al. [104]	Norway	2007	44%
Holt et al. [152]	US	2008	23%
McKinlay et al. [107]	New Zealand	2008	9%
Our Study	Morocco (Marakech)	2019	14%

It is possible, however, that psychotic manifestations, hallucinations especially might be underestimated given the tolerability of symptoms. Patients could deny their experience of hallucinations for fear of being branded insane[153].

Patients reporting hallucinations had a longer duration of disease than patients without hallucinations. That the difference only approached statistical significance could be explained by a small sample size. A similar finding was made by Pacchetti et al. [154] and Papapetropoulos et al.[153]. We found no relation between hallucinations and age or age of onset. The literature on hallucinations reports inconsistent results on age or age of onset[155 – 7]. **(TABLE XIII)**

TABLE XIII : Comparison of Age, Onset and Duration in Patients with Hallucination and Patients without Hallucinations

Study	Place	Year	Age (p)	Onset (p)	Dur (p)
Aarsland et al.[156]	Norway	1999	78.8±6.5 (0.003)	68.5±9.2 (0.2)	10.3±5.4 (0.13)
Sanchez-Ramoz et al.[155]	USA	1996	70±10.3 (0.007)	--	8.6±5.6 (0.008)
Pacchetti et al.[154]	Italy	2005	--	60.8±9.8 (NS)	10.3±5.55 (0.0001)
Paleacu et al.[158]	Israel	2005	76±7 (0.0001)	--	7.8±5.2 (NS)
Papapetropoulos et al.[153]	Greece	2005	--	57.63±10.4 (0.79)	8.55±6.3 (0.0001)
Fenelon et al.[157]	France	2000	73.9±7 (0.0001)	61.2±11 (NS)	12.9±7.5 (0.0001)
Our Study	Morocco (Marrakech)	2018	58.94±10.76 (0.461)	52.46±9.10 (0.967)	7.89±4.26 (0.057)

Psychotic symptoms, it has been pointed out, are a marker of quality of life in patients with Parkinson's disease[159]. We, however, could not reproduce this finding in our sample. This is probably due to the limited size of our sample. Psychosis has been shown to be associated with higher mortality in Parkinson's disease[160].

Psychotic symptoms caused some level of distress in up to 50% of caregivers of psychotic patients. Patients with psychosis are more likely to be placed in nursing homes[161].

In addition, the majority of our patients with hallucinations (78%) reported a stagnation of symptoms with L-Dopa. The remaining 22% reported a worsening of symptoms with L-Dopa.

4. Apathy in our Patients

Apathy was found in 16% of our sample. This places apathy among the least frequent neuropsychiatric symptoms in our sample. Our findings seem to be much smaller than prevalence rates in the literature: 54% in Aarsland et al.[104], and 28% in McKinlay et al[107]. **(TABLE XIV)**

TABLE XIV : Comparison of the Prevalence of Apathy with Other Studies

Study	Place	Year	Prevalence
Aarsland et al.[104]	Norway	2007	54%
McKinlay et al. [107]	New Zealand	2008	28%
Oguru et al. [162]	Japan	2010	60%
Benito et al. [163]	Spain	2012	22%
Our Study	Morocco (Marrakech)	2019	16%

Older patients and patients with longer duration of disease were more likely to report apathy or severer forms of it. Clark et al. found in their study an association with older age as in our study. However, contrary to our findings they found as association with the female gender and cognitive impairment [164].

Apathy caused some level of distress in nearly a third (31%) of caregivers of patients reporting apathy. Apathy creates a stigma, impairs quality of life and activities of daily living [165], and influences quality of life [166 – 7].

We did not, however, find any correlation between apathy and quality of life which could be attributed to a small sample size.

Response to treatment was mediocre with only 63% of symptomatic patients reporting improvement with L-dopa.

5. Behavioral Symptoms in our Patients

We found impulse control symptoms to be present in up to 23% of our patients. **(TABLE XV)**

TABLE XV : Prevalence of Impulse Control Symptoms in our Sample compared with other studies

Study	Place	Year	Prevalence
Tomer et al. [166]	Israel	1993	57%
Maia et al.[167]	Brazil	2003	17%
Siri et al. [168]	Italy	2010	58%
Attar et al. [169]	Morocco(Casablanca)	2015	16%
Our Study	Morocco(Marrakech)	2019	23%

With respect to the specific case of dopamine dysregulation syndrome, we observed a prevalence of 17.2%. **(TABLE XVI)**

TABLE XVI : Prevalence of Dopamine Dysregulation Syndrome in our Sample compared with other studies

Study	Place	Year	Prevalence
Giovannoni et al.[170]	UK	1999	4.1%
Pezzella et al. [171]	Italy	2005	3.5%
Attar et al. [169]	Morocco (Casablanca)	2015	11%
Our study	Morocco (Marrackech)	2019	17.2%

Known risk factors of impulse control symptoms in the literature includemale gender, early-onset Parkinson's disease, novelty seeking and impulsivity personality traits, personal or immediate family history of alcoholism, comorbid depression, or family history of psychiatric illness [172].

For our part, we found no statistically significant difference between patients with impulse control issues and those without in terms of age ($p = 0.66$), age of onset ($p = 0.70$), duration ($p = 0.09$), and L-dopa dose ($p = 0.36$). There was no difference either with respect to quality of life ($p=0.593$).

The majority of our patients (83.33%) reported a worsening of symptoms with L-Dopa.

III. Methodological Limitations in Our Study

1. Our study was conducted in a "hospital-clinical population" which might have introduced a selection bias in the study. For example, the majority of our patients were rural dwellers. This is an inadvertent reality in most studies and requires caution in interpreting findings. A community-based study would be the solution to this bias.
2. We used no control group in our study. However, the high prevalence of symptoms in our patients was evidently outside the norms for a healthy population.
3. Our sample was too heterogeneous. We did not exclude patients with cognitive impairment or patients who were under deep brain stimulation. Thus, some peculiarities of subgroups might have confounded general results.
4. We depended on caregivers for Neuropsychiatric inventory and on patients for treatment response. This was bound to result in incongruities in findings. However, we point out that not exactly the same symptoms were investigated in the two questionnaires, each one of which served a specific purpose in the study thus giving a more complete picture of patient condition.
5. The use of a telephone interview was probably not the best choice. It was however the only way we could evaluate a number of the patients who lived very far or who were unwilling to come in for consultation.
6. We used a relatively small sample to investigate the quality of life.
7. The questions had to be translated to the local language of patients. Very often, patients and caregivers found it difficult to understand.
8. We did not consider general risk factors of psychiatric manifestations.

RECOMMENDATIONS

Based on our findings, we suggest the following recommendations:

1. The search for neuropsychiatric manifestations should be included in the systematic evaluation of patients with Parkinson's disease at each medical visit.
2. Caregivers should be questioned about the presence of symptoms in patients.
3. Patients and their caregivers should be systematically questioned about the presence of adverse effects of medication.
4. Adjunct therapy specifically aimed at neuropsychiatric manifestations should be considered in patients with symptoms.
5. Caregivers should be educated on the role of the psychosocial environment in the occurrence and control of neuropsychiatric manifestations.
6. More research should be done in view of identifying risk factors of Parkinson's disease, and of neuropsychiatric manifestations in Parkinson's disease.
7. Work should be done on a translated version of psychometric tests in the local languages of our patients.

CONCLUSION

The neuropsychiatry of Parkinson's disease remains an interesting dimension of the disease. It has long been known that the spectrum of Parkinson's disease extends far beyond the obvious motor abnormalities indicating extrapyramidal involvement. The neuropsychiatry of Parkinson's disease is interesting because apart from the growing evidence of the intrinsic neuropathological basis with motor symptoms, they are quite frequent in the condition, and might actually predate motor signs. In fact, this could lead to many patients being followed up several years for apparently "non-parkinsonian" symptoms before the eventual expression of "parkinsonian" motor symptoms. This could be a factor of frustration, first, for the constant referrals from specialist to specialist, until the ultimate diagnosis of the condition with a "life-sentence" twist of the degenerative mechanism of the disease. These patients are elderly, are generally dependent, and have the cumulative effect of age, that is, they tend to be bearers of multiple pathologic conditions, and are polymedicated. The very demographical peculiarity of Parkinson's disease makes it an interesting disease because taking care of these patients tends to fall to the younger, more autonomous family members.

Another reason why the neuropsychiatry of Parkinson's disease is interesting is that it contributes considerably to the quality of life (QoL) of these patients. This means that any management protocol that ignores the deployment of the complete medical arsenal available at any given time as well for the motor symptoms as for the non motor symptoms would be an incomplete, and invariably, unsuccessful venture. That being said, the intrications of medication is worth noting because while treatment is geared toward the control of symptoms, it might as well be the cause of some symptoms, both motor and non motor. This calls for careful adjustment of doses to remain effective in controlling symptoms while averting complications. This makes the treatment of Parkinson's disease tricky, and patient-specific tailoring of doses as well as monitoring crucial. And, this certainly goes beyond the individual efforts of the physician. Managing Parkinson's disease requires the joint efforts of the physician, the caregivers and the patients.

The place of the caregiver is irreplaceable. The psychosocial environment is particularly of interest in this case. Though compelling evidence abounds to the biology of the neuropsychiatric manifestations of Parkinson's disease, the constant variability of findings points to several other factors being involved in the pathogenesis of the condition. While research still continues, it is evident the psychosocial environment is invariably of interest here. A warm, understanding and supportive entourage would go a long way to palliate the effects of biology, and ensure a stable mental and emotional state of patients.

ANNEX

I. Genetic and Molecular Mechanisms of Parkinson's Disease

Characteristic features of Parkinson's disease include neuronal loss in specific areas of the substantia nigra and widespread accumulation of α-synuclein, an abnormal intracellular protein (Fig 64). Although neither the loss of pigmented dopaminergic neurons in the substantia nigra[173 – 4] nor the deposition of α-synuclein in neurons is specific for Parkinson's disease, these two major neuropathologies are specific for a definitive diagnosis of idiopathic Parkinson disease when applied together.

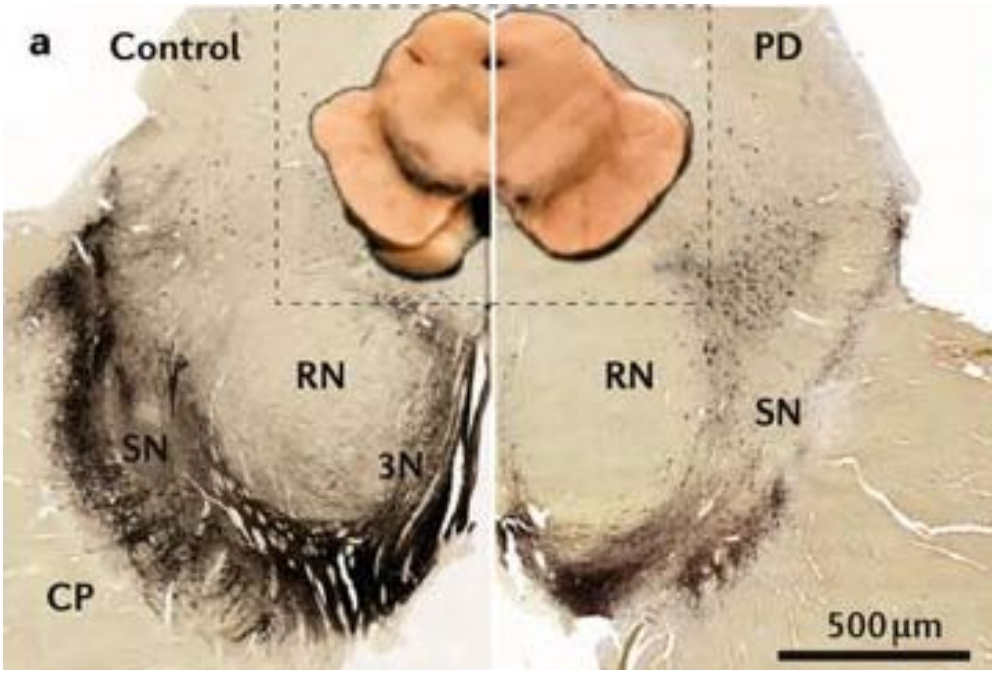

FIG 64. A transverse section of the midbrain depicting depigmentation of substantia nigra (SN) in Parkinson's disease (PD) on the right panel as compared to a control on the left panel. 3N,3rd nerve fibres; CP,cerebral peduncle; RN,red nucleus

α-synuclein aggregate to form Lewy bodies in the cytoplasm of remaining neurons. **(FIG 65) (FIG 66)**

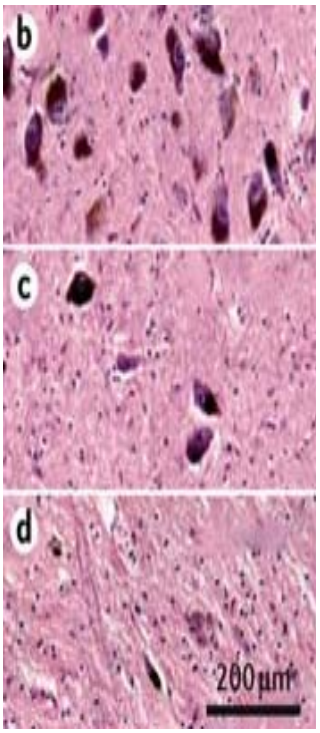

FIG 65 b-d | Haematoxylin and eosin staining of the ventrolateral region of the substantia nigra showing a normal distribution of pigmented neurons in a healthy control (part b) and diagnostically significant moderate (part c) or severe (part d) pigmented cell loss in Parkinson's disease.

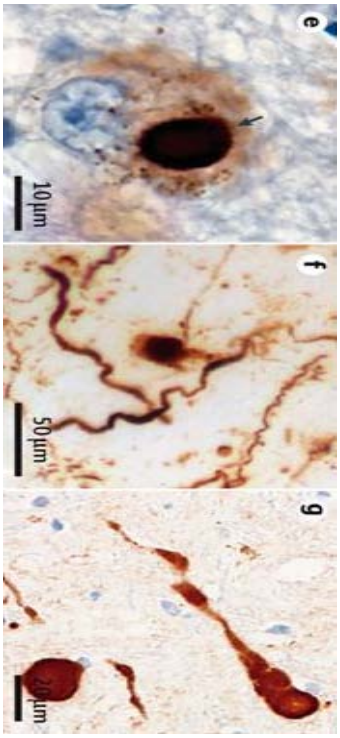

FIG 66 e-g | Immunohistochemical staining of α-synuclein shows the round, intracytoplasmic Lewy bodies (arrow in part e), more diffuse, granular deposits of α-synuclein (part e and part f), deposits in neuronal cell processes (part f), extracellular dot-like α-synuclein structures (part f) and α-synuclein spheroids in axons (part g).

The Lewy pathology initially occurs in cholinergic and monoaminergic brainstem neurons and in neurons in the olfactory system, but is also found in limbic and neocortical brain regions with disease progression (Fig.74).

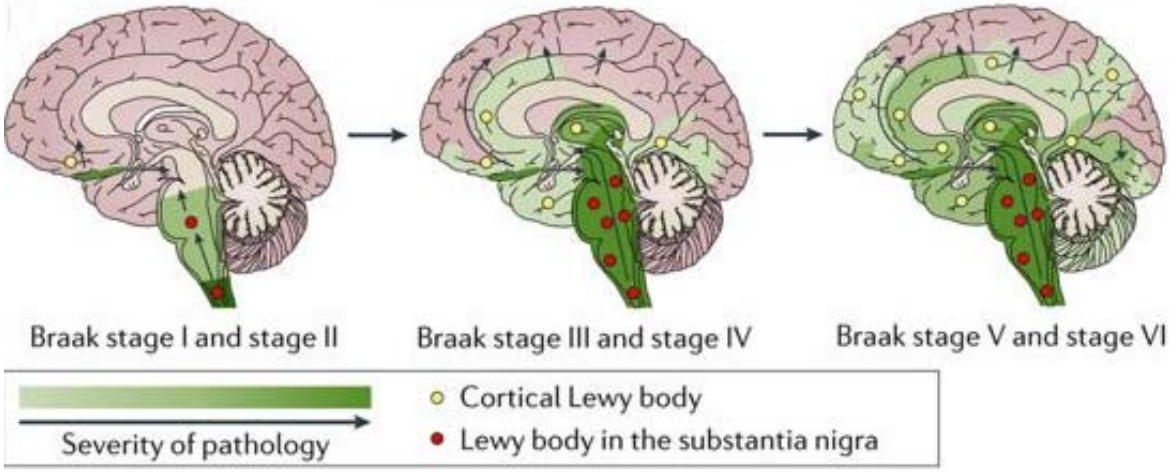

FIG 67. The theorized progression of α-synuclein aggregation in PD without Alzheimer pathology. α-Synuclein inclusions occur in cholinergic and monoaminergic lower brainstem neurons in asymptomatic cases (Braak stage I and stage II), infiltrate similar neurons in the midbrain and basal forebrain in those with the motor symptoms of PD (Braak stage III and stage IV), and then are found later in limbic and neocortical brain regions with disease progression (Braak stage V and stage VI)

Examples of these pathways are: (1) α-synuclein proteostasis, (2) mitochondrial function, (3) oxidative stress, (4) calcium homeostasis, (5) axonal transport and (6) neuroinflammation.

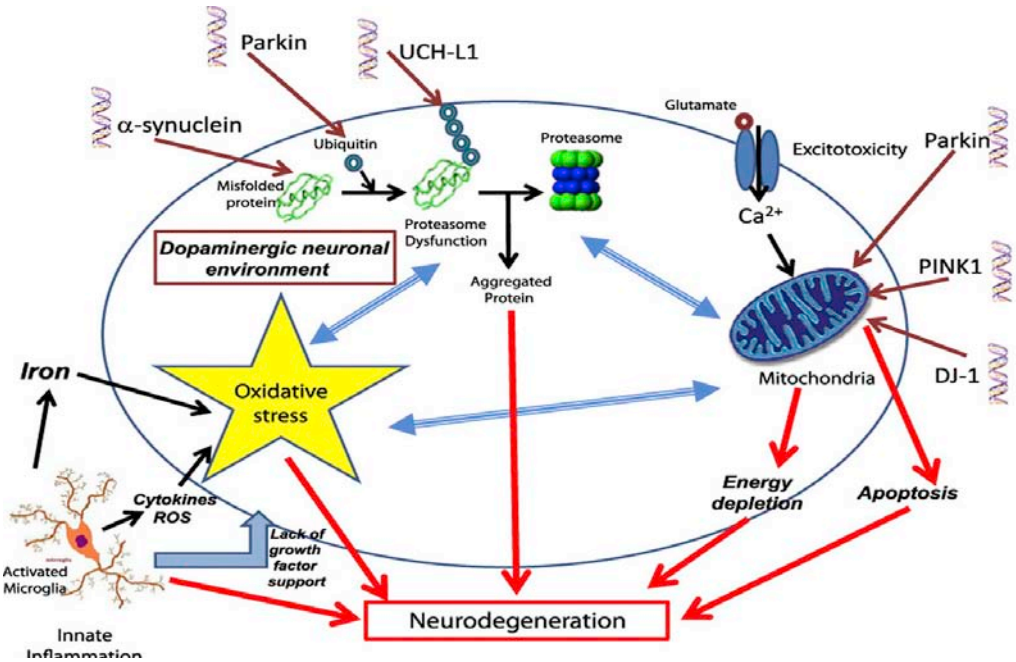

FIG 68. Molecular mechanisms of neurodegeneration in Parkinson's disease

1. Pathophysiology of Motor Symptoms

The basal ganglia are part of several parallel, but anatomically segregated thalamo-cortico-basal ganglia circuits, which have important functions in the control of actions and goal-directed behavior. These circuits are anatomically characterized by a strong convergence of cortical input onto relatively few subcortical output neurons and back to the cortex, suggesting a 'filter-like' function. Four circuits with a functionally similar, yet topographically distinct, organization have been identified to subserve limbic, prefrontal-associative, oculomotor and motor functions by linking the corresponding frontal cortical areas and subregions of the thalamus and basal ganglia[175 - 6]. Parkinsonism results from a decreased dopaminergic transmission in the motor region of the striatum with opposing effects on the direct and indirect pathways, which results in increased γ-aminobutyric acid (GABA)-ergic inhibition of thalamocortical projections (Fig. 76).

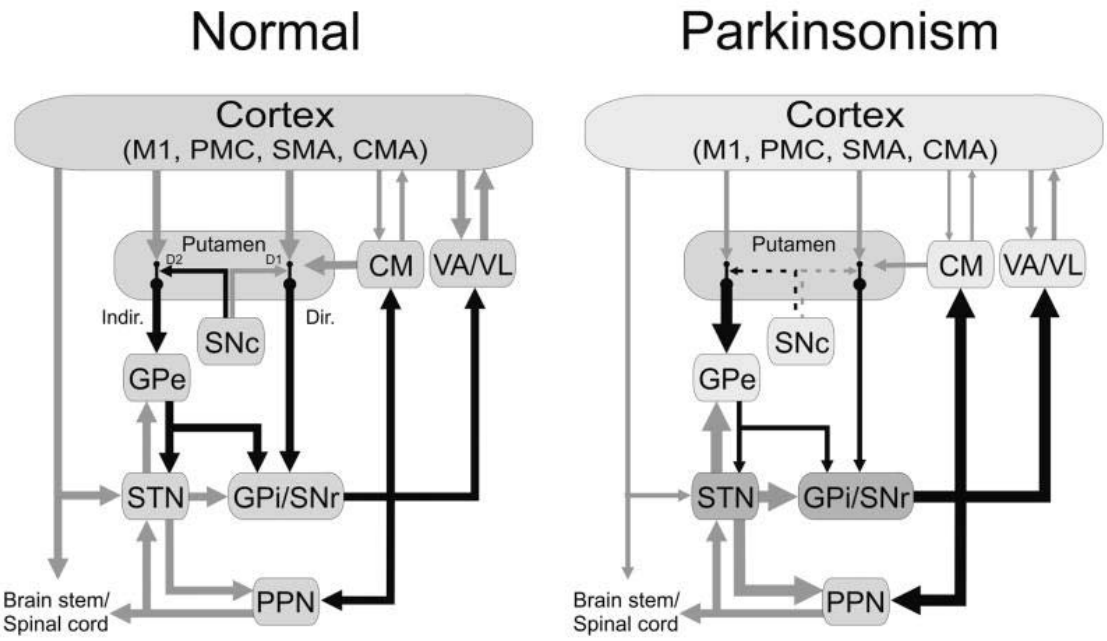

FIG. 69 Parkinsonism-related changes in overall activity ('rate model') in the basal ganglia-thalamocortical motor circuit. Black arrows indicate inhibitory connections; gray arrows indicate excitatory connections. The thickness of the arrows corresponds to their presumed activity. Abbreviations: CM, centromedian nucleus of thalamus; CMA, cingulate motor area; Dir., direct pathway; D1, D2, dopamine receptor subtypes; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; Indir., indirect pathway; M1, primary motor cortex; Pf, parafascicular nucleus of the thalamus; PMC, premotor cortex; PPN, pedunculopontine nucleus; SMA, supplementary motor area; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA, ventral anterior nucleus of thalamus; VL, ventrolateral nucleus of thalamus.

II. Pathophysiology of Neuropsychiatric Symptoms

The pathophysiology of the neuropsychiatric manifestations of Parkinson's disease is complex and not well delineated. These symptoms are caused by mechanisms that go beyond the motor basal ganglia [177], extending beyond the sole loss of dopaminergic neurons. What is known is that several other neurotransmitters are affected. As such degeneration of serotonergic, dopaminergic, noradrenergic, and cholinergic nuclei in the brainstem[178] would explain the neuropsychiatric manifestations in the disease. Several other cotical and sub cortical brain areas and neural pathways are involved in the pathogenesis of these symptoms.

According synuclein staining of the locus ceruleus (noradrenergic) and raphe nuclei (serotoninergic) preceding the to Braaks hypothesis of a rostral-caudal progression of pathology, with α- earliest changes seen in the substantia nigra [177], it makes sense that the earliest symptoms of Parkinson's disease, rather than being motor, would be non motor symptoms. In fact, it is known that neuronal loss in the locus ceruleus may be even more severe than in the substantia nigra [179]. The precedence of motor symptoms by non motor symptoms, and the higher prevalence of neuropsychiatric symptoms in Parkinson's disease than in the general population point to this biological substrate.

As the pathology progresses, more and more symptoms add up, and cognitive involvement eventually becomes patent with cortical involvement.

Although the above data provide some insight into potential pathophysiological explanations for neuropsychiatric symptoms in Parkinson's disease, much is left to learn. Many individuals do not develop some symptoms in spite of similar pathophysiological abnormalities. Thus, the etiology of these neuropsychiatric symptoms in Parkinson's disease is likely multifactorial with contributions from biology as well as psychosocial factors including personality, individual coping strategies, and availability of social supports [180].

III. Pathophysiology of Fluctuations

1. Motor Fluctuations

At the initiation of levodopa therapy, two types of therapeutic responses are present: the short-duration response (SDR) and the long-duration response (LDR) [181]. The short duration response depends on the pharmacokinetics of levodopa, and is short-lived (a few hours). Meanwhile, the long-duration response maintains a sustained control of symptoms for a much longer time, and ensures a smooth effect of treatment. Fluctuations are the manifestation of a long-duration response gradually lost leaving only the short-duration response to control symptoms. This leads to short-lived peaks, and alternating improvement of symptoms corresponding to fluctuations.

Also, a pre synaptic loss of dopaminergic neurons robs the striatum of its storage function, and the inability to buffer dopamine concentration fluctuations in the blood. Furthermore, gene alterations and protein anomalies in the post synaptic apparatus contribute to fluctuations.

In addition in the process of neurodegeneration, when the tonic dopaminergic release (passive stabilization) is outdone, the introduction of exogenous levodopa causes a pulsatile stimulation of receptors.

Finally, fluctuations could be linked to any process altering the availability of levodopa to the brain: swallowing problems, delayed gastric emptying due to high acidity, altered absorption with high protein meals and the presence of Helicobacter pylori[182 – 8].

2. Non Motor Fluctuations

There is evidence suggesting that dopamine denervation is key in non motor fluctuations [189]. However, it is known that serotonergic, noradrenergic and cholinergic pathways contribute to the appearance of non-motor symptoms in Parkinson's disease [190]. The interaction between dopamine oscillations and the other neurotransmitters could explain non motor fluctuations[191].

IV. Clinical Feature and Diagnosis

1. Idiopathic Parkinson's Disease

Parkinson disease is clinically defined by the presence of bradykinesia and at least one additional cardinal motor feature (rigidity or rest tremor), as well as additional supporting and exclusionary criteria[9 – 12] (Annex IV, 1). Onset of motor symptoms is usually unilateral and asymmetry persists throughout the disease. The average age of onset is in the late fifties but could occur before 40 years of age. Young-onset Parkinson disease occurs before 45 years, and Juvenile Parkinson's disease occurs before 21 years [192 – 3].

In addition to the cardinal motor features, a majority of patients with Parkinson disease also have non-motor symptoms at the time of diagnosis [193]. Non-motor symptoms involve a multitude of functions, including disorders of sleep-wake cycle regulation, cognitive impairment (including frontal executive dysfunction, memory retrieval deficits, dementia and hallucinosis), disorders of mood and affect, autonomic dysfunction (mainly orthostatic hypotension, urogenital dysfunction, constipation and hyperhidrosis), as well as sensory symptoms (most prominently hyposmia) and pain [193].

Differential diagnoses of Idiopathic Parkinson's disease are multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and, corticobasal degeneration (CBD). Clinically, it is important to distinguish Idiopathic Parkinson's disease from essential tremor, drug-induced parkinsonism and vascular parkinsonism[10]. Accuracy of a clinical diagnosis of Parkinson disease can be improved by the stringent use of standard clinical criteria, such as the UK Parkinson's Disease Society Brain Bank (UKPDSBB) criteria, but even then diagnostic accuracy at first visit is only slightly above 80%, as shown by a recent meta-analysis of 11 studies assessing a UKPDSBB-based clinical diagnosis against post-mortem pathological examination as the gold standard[194]. Such findings highlight the need for diagnostic tests and biomarkers to enhance diagnostic confidence in early disease, or to eventually diagnose Parkinson disease in its prodromal stages.

2. Neuropsychiatric Symptoms

The diagnosis of neuropsychiatric manifestations is clinical. It follows from interrogation of patients and their caregivers. The diagnosis could, however, be tricky seeing as there is often the overlapping of motor symptoms with somatic symptoms. This is particularly the case when dealing with sleep, appetite/weight, and energy disturbance and psychomotor change. This makes the Diagnostic and Statistical Manual of Psychiatric Disorders, 4th Edition (DSM IV) criteria[195] difficult to apply. Different approaches have been proposed to deal with these challenges[196].

When it comes to research, several scales have been prepared and validated for use. There are the general scales such as the Neuropsychiatry Inventory (NPI), and the more specific scales for specific diagnoses: the Beck Depression Inventory (BDI) for depression; the Hospital Anxiety and Depression Scale (HADS) for anxiety; the National Institute for Neurological Disorders/ the National Institute of Mental Health (NIND/NIMH) Parkinson's disease psychosis criteria for psychosis; the Apathy Scale (AS) for apathy; the Delayed Alternation task (DAT) for impulse control disorder.

V. Management

1. Dopaminergic pharmacological targets

1.1. L-Dopa

L-Dopa has remained the gold standard for Parkinson disease and parkinsonism, and over time, practically all patients with Parkinson disease will require treatment with this agent[197]. L-Dopa is a precursor to dopamine, and is capable of crossing the blood-brain barrier. It has a short half-life and of varying gastro-intestinal absorption. L-Dopa causes symptom fluctuations and motor dyskinesia in patients.

1.2. Catechol-O-methyltransferase inhibitors

Current L-Dopa preparations include inhibitors of aromatic amino acid decarboxylase such as carbidopa or benserazide to prevent peripheral metabolism of dopamine and enhance bioavailability. As a consequence, the peripheral metabolism of L-Dopa is shifted towards the activity of a secondary metabolic pathway that involves ortho-methylation of L-Dopa via catechol-*O*-methyltransferase (COMT). Inhibition of this enzyme in the periphery will further enhance bioavailability and the half-life of L-Dopa, which is of particular benefit in patients who have developed motor fluctuations of the wearing-off type[198]. Extending the duration of effect of individual L-Dopa doses via COMT inhibitors has become a first-line treatment in these individuals[199].

1.3. Monoamine oxidase type B inhibitors

Oxidation via monoamine oxidase type B (MAOB) in glial cells is a major clearance mechanism for synaptically released dopamine, next to presynaptic reuptake via the dopamine transporter[200]. Inhibition of MAOB prolongs and increases synaptic dopamine concentrations. Two such inhibitors, selegiline and rasagiline, are termed 'suicide' inhibitors of MAOB due to their irreversible action. Conversely, safinamide acts as a reversible MAOB inhibitor[201].

1.4. Dopamine agonists

The actions of dopamine on striatal medium spiny neurons are mediated via two classes of dopamine receptors. Dopaminomimetics with direct activity to dopamine receptors (dopamine receptor agonist) mainly target the D2 receptor family. An important advantage of dopamine agonists is their longer half-life than L-Dopa, which makes them attractive candidates as adjunct therapies in patients with motor fluctuations[199]. In addition, rotigotine is available as a transdermal patch formulation that affords continuous drug delivery. Overall, dopamine agonists are believed to induce less pulsatile striatal dopamine receptor stimulation than L-Dopa and this is taken as an explanation for the markedly reduced risk to induce motor complications when dopamine agonists are used as initial monotherapy in Parkinson disease[202]. Drawbacks include their reduced overall effect size as compared with L-Dopa and their potential to induce drowsiness and impulse control issues.

2. Non-dopaminergic pharmacological targets

With growing knowledge on the other neural pathways implicated in the genesis of symptoms, as well as the complications of dopamine therapy, other pharmacological agents have been synthesized to meet the need of controlling symptoms. An example, amantadine is an *N*-methyl-d-aspartate receptor antagonist and used for the treatment of L-Dopa induced dyskinesia[199]. Cholinesterase inhibitors can have striking beneficial effects on the cognitive disturbances of patients with Parkinson disease who also have dementia, an effect that is possibly related to the considerable loss of cholinergic projections from the nucleus basalis of Meynert[199]. The most effective therapy for psychotic symptoms in Parkinson disease is clozapine[203]. Finally, autonomic dysfunction is extremely common, particularly in late-stage Parkinson disease, and pharmacological therapies are largely directed at autonomic nervous system targets. They include the mineralocorticoid fludrocortisone and adrenergic agents (such as midodrine and etilefrine), the noradrenaline precursor (that is, droxidopa) to treat orthostatic hypotension, antimuscarinics (such as oxybutynin, tolterodine or trospium chloride) for urinary urgency or incontinence, and pro-kinetic drugs (such as macrogol or lubiprostone) to improve constipation[202].

3. Deep Brain Stimulation

Deep brain stimulation is based on the finding that high-frequency (100-200 Hz) electrical stimulation of specific brain targets can mimic the effect of a lesion without the need for destroying brain tissue and involves the implantation of an electrode in brain tissue. The stimulation-induced improvement is linked to the previous treatment response to l-DOPA, that is, patients with motor symptoms who do not respond to dopaminergic treatment are unlikely to respond to DBS. In general, ideal candidates have idiopathic Parkinson disease with an excellent l-DOPA response but motor complications due to long-term medical treatment[204]. Dementia, acute psychosis and major depression are exclusion criteria. Patients with young-onset Parkinson

disease fulfil the inclusion criteria for DBS best and are overrepresented among the operated group. Several randomized controlled trials have proven that DBS provides a better QOL than best medical management in patients with clinically relevant motor fluctuations and dyskinesia[205]. DBS is a complex therapy that requires a high level of interdisciplinary expertise in the correct surgical placement of the electrode, postoperative programming and the adjustment of neurostimulation and drug therapy[204]. The most relevant adverse events are intracranial bleedings and device complications (such as infections and lead misplacements, among others), which account for a permanent morbidity of over 1–3%.
The mortality of DBS is less than 0.5%[206]. Thus, the benefit–risk profile of DBS is usually considered to be favorable, in particular, with respect to the large gains in QOL compared with best medical management observed in clinical trials. Psychiatric sequelae of DBS (for example, apathy, depression, impulsiveness or mania) are not uncommon and result from a complex interplay between disease-related psychiatric symptoms, dopaminergic imbalance due to the profound medication changes and stimulation-induced effects on limbic basal ganglia circuits[207].

VI. TOOLS

1. MDS Clinical Diagnostic Criteria for Parkinson's disease –Executive Summary/ Completion Form

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's Disease Rating Scale. Once parkinsonism has been diagnosed:

Diagnosis of Clinically Established Parkinson's disease requires:

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

Diagnosis of Clinically Probable Parkinson's disease 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 Parkinson's Disease:

- ☐ 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 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 Parkinson's Disease

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 hypotension32—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

Criteria Application:

1. Does the patient have parkinsonism, as defined by the MDS criteria? Yes ☐ No ☐
   If no, neither probable PD nor clinically established PD can be diagnosed. If yes:
2. Are any absolute exclusion criteria present? Yes ☐ No ☐
   If "yes," neither probable PD nor clinically established PD can be diagnosed. If no:
3. Number of red flags present ____
4. Number of supportive criteria present ____
5. Are there at least 2 supportive criteria and no red flags? Yes ☐ No ☐
   If yes, patient meets criteira for clinically established Parkinson's disease. If no:
6. Are there more than 2 red flags? Yes ☐ No ☐
   If "yes," probable PD cannot be diagnosed. If no:
7. Is the number of red flags equal to, or less than, the number of supportive criteria? Yes ☐ No☐
   If yes, patient meets criteria for probable Parkinson's disease

2. NPI Questionnaire

Please answer the following questions based on changes that have occurred since the patient first began to experience memory problems.

Circle "Yes" only if the symptom(s) has been present in the last month. Otherwise, circle "No". For each item marked "Yes":

a) Rate the SEVERITY of the symptom (how it affects the patient):

1 = Mild (noticeable, but not a significant change)
2 = Moderate (significant, but not a dramatic change)
3 = Severe (very marked or prominent, a dramatic change)

b) Rate the DISTRESS you experience due to that symptom (how it affects you):

0 = Not distressing at all
1 = Minimal (slightly distressing, not a problem to cope with)
2 = Mild (not very distressing, generally easy to cope with)
3 = Moderate (fairly distressing, not always easy to cope with)
4 = Severe (very distressing, difficult to cope with)
5 = Extreme or Very Severe (extremely distressing, unable to cope with)

Please answer each question carefully. Ask for assistance if you have any questions.

Delusions	Does the patient have false beliefs, such as thinking that others are stealing from him/her or planning to harm him/her in some way?
Yes No	SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5
Hallucinations	Does the patient have hallucinations such as false visions or voices? Does he or she seem to hear or see things that are not present?
Yes No	SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5
Agitation/Aggression	Is the patient resistive to help from others at times, or hard to handle?
Yes No	SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Depression/Dysphoria Does the patient seem sad or say that he /she is depressed?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Anxiety Does the patient become upset when separated from you? Doeshe/she have any other signs of nervousness such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Elation/Euphoria Does the patient appear to feel too good or act excessively happy?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Apathy/Indifference Does the patient seem less interested in his/her usual activities or in the activities and plans of others?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Disinhibition Does the patient seem to act impulsively, for example, talking to strangers as if he/she knows them, or saying things that may hurt people's feelings?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Irritability/Lability Is the patient impatient and cranky? Does he/she have difficulty coping with delays or waiting for planned activities?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Motor Disturbance Does the patient engage in repetitive activities such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Nightime Behaviors	Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?	
Yes No	SEVERITY: 1 2 3	DISTRESS: 0 1 2 3 4 5
Appetite/Eating	Has the patient lost or gained weight, or had a change in the type of food he/she likes?	
Yes No	SEVERITY: 1 2 3	DISTRESS: 0 1 2 3 4 5

3. Questionnaire on Therapeutic Response

NEUROPSYCHIATRIC DISORDERS IN PARKINSON'S DISEASE
Patient Name:
Date of Birth:
Sex : M ☐ F ☐
Diagnosis : Yes ☐ No ☐
Other Diseases : Yes ☐ No ☐
If yes specify :…….

PATIENT HISTORY
Duration of Parkinson's disease:
On-going treatments :

- Modopar : Yes☐ No☐

Daily dose:

- Other treatments : Yes☐ No☐

If yes specify :…….

Neuropsychiatric disorders:

	Off Period		L-dopa	
Depression:	Yes ☐	No ☐	Yes☐	No ☐
• Sadness :	Yes ☐	No ☐	Yes☐	No ☐
• Pessimistic ideation :	Yes ☐	No ☐	Yes ☐	No ☐
• Reduced sleep :	Yes ☐	No ☐	Yes ☐	No ☐
• Loss of appetite :	Yes ☐	No ☐	Yes ☐	No ☐

• Weeping :	Yes ☐	No ☐	Yes ☐	No ☐
• Suicidal thoughts :	Yes ☐	No ☐	Yes ☐	No ☐
Anxiety :	Yes ☐	No ☐	Yes ☐	No ☐
•Sensation of being out of breath:	Yes ☐	No ☐	Yes ☐	No ☐
•Nervousness :	Yes ☐	No ☐	Yes ☐	No ☐
•Fear :	Yes ☐	No ☐	Yes ☐	No ☐
•Abdominal discomfort:	Yes ☐	No ☐	Yes ☐	No ☐
Panic Attacks :	Yes ☐	No ☐	Yes ☐	No ☐
•Increased heart rate :	Yes ☐	No ☐	Yes ☐	No ☐
•Difficulty breathing :	Yes ☐	No ☐	Yes ☐	No ☐
•Chest pains :	Yes ☐	No ☐	Yes ☐	No ☐
•Dizziness :	Yes ☐	No ☐	Yes ☐	No ☐
•Transpiration :	Yes ☐	No ☐	Yes ☐	No☐
Apathy :	Yes ☐	No ☐	Yes ☐	No☐
• Loss of interest :	Yes ☐	No ☐	Yes ☐	No☐
• Loss of initiative :	Yes ☐	No ☐	Yes ☐	No☐
• Lack of emotion :	Yes ☐	No ☐	Yes ☐	No☐
Psychoses :				
• Visual hallucinations:	Yes ☐	No ☐	Yes ☐	No ☐
• Auditory hallucinations:	Yes ☐	No ☐	Yes ☐	No ☐
• Olfactory hallucinations:	Yes ☐	No ☐	Yes ☐	No ☐
• Hypnagogic hallucinations:	Yes ☐	No ☐	Yes ☐	No ☐
• Hypnopompic hallucinations:	Yes ☐	No ☐	Yes ☐	No ☐
Dopamine Dysregulation Syndrome				
• Impulsions	Yes ☐	No ☐	Yes ☐	No ☐
• Hyperphagia	Yes ☐	No ☐	Yes ☐	No ☐
• Addiction	Yes ☐	No ☐	Yes ☐	No ☐

4. PDQ-8 Questionnaire

PDQ-8 QUESTIONNAIRE
NAME:.....
AGE: DURATION:
LATERALITY:
TREATMENT:

	Never	Occasionally	Sometimes	Often	Always or cannot do at all
1. Had difficulty getting around in public?					
2. Had difficulty dressing yourself?					
3. Felt depressed?					
4. Had problems with your close personal relationships?					
5. Had problems with your concentration, e.g. when reading or watching TV?					
6. Felt unable to communicate with people properly?					
7. Had painful muscle cramps or spasms?					
8. Felt embarrassed in public due to having Parkinson's disease?					

VII. COMMENTS AND QUESTIONS PUT FORWARD BY JUDGES

Pr. F. MANOUDI

1. I see from the page 6 that you included all the patients: patients diagnosed from a long time and those diagnosed recently, diagnosed only the day before, for example. Wouldn't that constitute a methodological bias?
   ans. It is actually an oversight because it was one of the things we paid attention to. From our research in the literature, we realized it was best to include patients diagnosed at least 6 months before the research. The shortest duration after diagnosis in our sample was exactly 6 months so we did not have problems here. We are going to rectify it in our methodology.
2. You did not look for history of psychosis in the patients because we would like to know if these patients have some sort of genetic vulnerability to psychotic manifestations than other populations.
   ans. It is true we did not investigate the history of psychosis in our patients. In fact, we would have liked to investigate not only a history of psychosis but also of mood disorders seeing as several research findings point to a possible causal link between depression/ anxiety and Parkinson's disease. We hope to do that in the next work on Parkinson's disease.
3. Since you used the NPI, you couldn't make diagnoses. For depression, for example, you'd require specific diagnostic tools such as the DSM 5 or the BDI. But since you looked just for symptoms, write "depressive symptoms" instead of depression. The same goes for psychosis.
   ans. Yes, indeed, we sought for symptoms. Our research tools allowed only for identifying these symptoms but not for diagnoses.

Pr. H. GHANNANE

1. Since you specified in the methodology that you were dealing with idiopathic Parkinson's disease, I think it'd be better if you changed the title to Neuropsychiatric Manifestations in Idiopathic Parkinson's disease
   ans. Yes, indeed. The title must be modified.
2. You looked for a whole lot of information on patients from age to origins and health insurance but we'd have liked to know their level of education so we could know their capacity to answer ther questions.
   ans. Yes, we should have asked about the patients' level of education. A lot of the literature we consulted did that, and we hope that in the next research work we could add it.

3. You included about 44% of patients with co-morbidities like diabetes and high blood pressure, and we all know that these do have a psychological impact on patients. It would have been better to select only patients without co-morbidities.
   ans. It is true co-morbidities modify the psychological state of patients and worsen treatment outcomes. What we found in the literature points to a certain relation between Parkinson's disease and depression/ anxiety, which suggests an overlapping pathophysiology. There is a certain "epidemiological credence" to this overlapping pathophysiology suggesting that for the particular case of Parkinson's disease, these mood disorders are not simply reactional.
4. Did you include patients with deep brain stimulation? If yes, what is the impact of this treatment on the neuropsychiatric manifestations?
   ans. Yes, about 4 patients. It was a very small sample size to consider significant enough for any authentic results. This suggests how heterogeneous our sample was, and we hope next time to be more selective.

Pr. F. ASRI

1. Your questionnaire allowed you to look for symptoms, not diagnoses. So, in response to my friend (Pr. Manoudi) you were actually dealing with depression symptoms.

Pr. M. CHRAA

1. We had a feeling before the study that neuropsychiatric manifestations are quite frequent in our patients and that they have an impact on the quality of their lives. Now we have been able to prove these hypotheses.
2. We've also been able to show that the treatment we prescribe such as L-Dopa controls some symptoms but worsens some other symptoms.

ABSTRACTS

Abstract

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Classically described as a motor disorder, Parkinson's disease is far from being a "motor only" disorder. In fact, it is known that prior to the expression of motor symptoms due to degeneration of dopaminergic pathways in the pars compacta of the substantia nigra, several non motor symptoms are already present.

Our work sought to isolate the neuropsychiatric manifestations of Parkinson's disease and investigate how they were related to demographic characteristics, and the impact of these symptoms on the quality of life of our patients.

With a sample size of 79 patients, we found a slight male predominance (sex ratio: 1.19).Our patients were relatively younger (59.0 years), of recent diagnosis (6.5 years), and of unbiased age of onset (52.6 years) compared to other populations. Neuropsychiatric symptoms were present in 95% of our patients, with the most frequent being depression (77%), irritability (67%), anxiety (57%) and sleep disorders (52%).

Neuropsychiatric symptoms caused considerable distress for patients and caregivers. Depression was the only symptom that significantly impacted the quality of life of patients ($p=0.046$).

A gender-biased experience of symptoms was noted for patients and their caregivers. Symptoms were more frequent and much severer in females.

All in all, our patients reported worse quality of life outcomes compared to other populations. This points to the need for a holistic approach to the management of the disease. Also, the role of a conducive psychosocial environment is primordial. Further research is required to explain the vast disparities between our patients and others.

Résumé

La maladie de Parkinson est la seconde maladie neurodégénérative après l'Alzheimer. Classiquement décrite comme un trouble moteur, la maladie de Parkinson est loin de d'être qu'une trouble isolément moteur. En fait, on sait qu'avant l'apparition des signes moteurs due à la dégénération dopaminergique dans la pars compacta de la substance noire, plusieurs signes non moteurs seront déjà présents.

Notre travail avait comme but l'isolement de ces manifestations neuropsychiatriques de la maladie, et l'investigation des relations avec la démographie et leur impact sur la qualité de vie de nos patients.

Avec un effectif de 79 patients, nous avons mis en évidence une légère prédominance masculine (sexe ratio : 1,19). Comparés à d'autres populations, nos patients étaient relativement jeunes (59 ans), diagnostiqués plus récemment (6,5 ans), avec un âge de début de 52,6 ans. Les troubles neuropsychiatriques étaient présents chez 95% des patients, les symptômes les plus fréquents étant la dépression (77%), l'irritabilité (67%), l'anxiété (57%) et les troubles de sommeil (52%).

Les troubles neuropsychiatriques sont source de détresse considérable chez les patients et leurs soignants. La dépression était le seul symptôme ayant un impact significatif sur la qualité de vie des patients ($p=0.046$).

Une expérience des symptômes liée au sexe a été constatée. Les symptômes étaient plus fréquents et plus sévères chez les femmes.

Au total, nos patients ont rapporté une qualité de vie pire que dans différentes populations. Ceci indique la place d'une approche globale dans la prise en charge de cette affection. En outre, la place d'un contexte psychosocial propice est incontournable. Plus de recherche serait nécessaire pour expliquer les vastes différences de nos patients des autres populations.

ملخص

يعد مرض الشلل الرعاش أو مرض باركنسون ثاني اضطراب تنكس عصبي شائع بعد مرض الزهايمر،والذي يوصف عادة بكونه اضطراب حركي.

غير أنه لا يمكن اعتبار مرض الشلل الرعاش اضطرابا حركيا محضا . كون أن مجموعة من الأعراض غير الحركية تظهر قبل الأعراض الحركية التي تنتج عن اضطراب في المسارات العصبية للدوبامين.

سعى عملنا إلى عزل الأعراض النفسية والعصبية لمرض الشلل الرعاش ودراسة ارتباطها بالخصائص الديموغرافية كماإظهار مدى تأثير هذه الأعراض على جودة حياة مرضانا.

شملت دراستنا 79 مريضا ، تميزت بغلبة طفيفة للذكور (نسبة الجنس ذكور/اناث تساوي 1.19).

كان مرضانا أصغر سنا (59.0 سنة) ، وحديثي التشخيص (ب 6.5 سنةو متوسط عمر في بداية المرض 52.6 سنة) مقارنة بالعينات الأخرى المدروسة .كما كانت الأعراض العصبية والنفسية موجودة عند 95 ٪ من مرضانا، و كانت حالات الاكتئاب الأكثر شيوعا (77 ٪) ، متبوعة بالتهيج (67 ٪) ،ثم القلق (57 ٪) واضطرابات النوم (52 ٪).

تسببت الأعراض النفسيةالعصبية في انزعاج لدى المرضى ومقدمي الرعاية .و كان الاكتئاب هو العارض الوحيد الذي أثر بشكل كبير على جودة حياة المرضى ($p = 0.046$).

كما لوحظ من خلال دراسةأخرى أن الأعراض كانت أكثر تواتراً و حدة عند الإناث.

عبر مرضانا بشكل عام عن جودة عيش أقل مقارنة بنظرائهم من عينات المرضى الأخرى المدروسة.هذا يشير إلى ضرورة اتباع نهج كلي و شامل في التعامل مع المرض,كون أن وجود بيئة نفسية واجتماعية مواتية له دور أساسي في تحسين جودة العيش. كما يجب القيام بأبحاث أخرى لشرح التباينات الشاسعة بين مرضانا والعينات الأخرى.

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أقْسِم بِالله العَظِيم

أن أراقبَ الله في مِهْنَتِي.

وأن أصُونَ حياة الإنسان في كآفّةِ أطوَارهَا في كل الظروف والأحَوال باذلا وسْعِي في استنقاذها مِن الهَلاكِ والمرَضِ والألَم والقَلَق.

وأن أحفَظَ لِلنَاسِ كرَامَتهُم، وأسْتر عَوْرَتهُم، وأكتمَ سِرَّهُمْ.

وأن أكونَ عَلى الدوَام من وسائِل رحمة الله، باذلا رِعَايَتي الطبية للقريب والبعيد، للصالح والطالح، والصديق والعدو.

وأن أثابر على طلب العلم، أسَخِّرَه لِنَفْعِ الإِنْسَان ..لا لأذَاه.

وأن أُوَقّرَ مَن عَلَّمَني، وأُعَلّمَ مَن يَصْغرَني، وأكون أخاً لِكُلِّ زَميلٍ في المِهنَةِ الطِّبِّيَة مُتعَاونِينَ عَلى البرِّ والتقوى.

وأن تكون حياتي مِصْدَاق إيمَاني في سِرّي وَعَلانيَتي، نَقِيَّة مِمّا يُشينهَا تجَاهَ الله وَرَسُولِهِ وَالمؤمِنين.

والله على ما أقول شهيدا

كليـــــــة الـطـب
و الصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH

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UNIVERSITÉ CADI AYYAD

سنة 2019 أطروحة رقم 199

المظاهر العصبية والنفسية
في مرض باركنسون

الأطروحة

قدمت ونوقشت علانية يوم **2019/07/11**

من طرف

السيد رايموند كليفور

المزداد في 07 يناير 1991 في غانا

لنيل شهادة الدكتوراه في الطب

الكلمات الأساسية:

مرض باركنسون - المظاهر النفسية العصبية - التقلبات

لام دوبا - جودة الحياة

اللجنة

السيد	ف. عسري أستاذ في الطب النفسي	الرئيس
السيد	م. شراع أستاذ في الفيزيولوجيا العصبية	المشرف
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