

Depression among Patients with Parkinson's Disease in a Nigerian Tertiary Hospital

Type of Article: Original

Olaitan Christiana Okunoye¹, God'spower Eshiofe Asekomeh²

¹Department of Internal Medicine, University of Port Harcourt Teaching Hospital and ²Chevron Clinic, Port Harcourt Rivers State, Nigeria.

ABSTRACT

BACKGROUND

There is increasing evidence that Parkinson's disease (PD) can cause depression. This dimension has not been sufficiently studied particularly among Nigerian Africans. Our aim was to determine the frequency and severity of depression among patients with PD and to compare this with their healthy counterparts.

METHODS

36 conservative patients with a clinical diagnosis of PD had the Beck Depression Inventory-II administered to them. A structured questionnaire interview and a neurological examination including the Hoehn and Yahr stage of illness scale and the motor section of the Unified Parkinson's Disease Rating Scale were performed. An equal number of age and sex matched controls were also recruited for the study.

RESULTS

Of the 36 PD patients, 83.3% had persistently low mood. Based on their Beck Depression Inventory score, 25% had mild depression, 18% had moderate depression and 16.7% had severe depression. Depression was worse with disease severity.

CONCLUSION

Patients with PD had a higher frequency of depression compared to their healthy counterparts. A multidisciplinary approach to the management of PD that includes depression-reducing interventions is required for this population of patients.

Keywords: Depression, Parkinson's disease, BDI-II

Correspondence: Dr. O.C. Okunoye

E-mail: olaitanok@gmail.com

INTRODUCTION

Depression is the most common non-motor symptom of PD [1]. It has been the focus of numerous research studies in PD [2-6]. Depression in the context of PD can be reactive, caused by the incurable, progressive nature of the disease, and therefore can be an understandable reaction to disease and its consequences [3]. On the other hand, there is a widespread and severe disruption of monoaminergic neurotransmission, predisposing to depression [7-9]. Depression in patients with PD should thus be treated as a single entity.

Depression is often overlooked by physicians because of the many shared clinical features between the two disorders, such as weight loss, sleep disturbance, fatigue, sexual dysfunction, forgetfulness, and bradykinesia. If the physician brings up the topic by asking specific depression-related questions, most patients will be honest and will discuss their mental state, although they often will not bring up "depression" themselves or identify the changes they are experiencing as depression [10].

Estimates of the incidence of comorbid depression vary widely, from 4% to 75% [11]. There are variations in incidence of depression in PD due to few epidemiological studies. The available surveys in research centres diagnose depression in 40% to 50% of patients with PD compared to community-based studies which have rates of depression that are less than 10% [1]. Rates of depression in PD have also been shown to vary widely between different countries. Surveys in Norway [1] and China [12] found the rates of major depression were 7.5% and 16.5% respectively.

The Global Parkinson's Disease Survey, which included 1000 patients, 200 clinicians, and 187 caregivers in five countries including the US, found that approximately half of PD patients had depressive symptoms that significantly impacted their daily functioning [13]. The fact that no African country was included in this study lends credence to the assertion that the exact frequency and pattern of depression among Africans has not been fully studied particularly in Africa.

It is known that in comparison to the general population, there is a considerable enhanced risk of depression in Parkinson's disease thus requiring that the physician screen all PD patients for depression [14]. Additionally, depression can impair both fine motor skills and cognitive function and is a primary factor negatively affecting HRQOL in PD [14].

Using the Beck Depression Inventory II (BDI-II)[15] as a psychometric measure of depression, this study set out to determine the frequency and severity of depression among Nigerians with PD presenting at the University of Port Harcourt Teaching Hospital. It will also relate the frequency and severity of depression to the stage and severity of PD. We hope that results from this study will serve as a basis for comparison with studies among PD patients from other population and help fill the void created by a dearth in literature of studies on depression among Parkinson's disease patients in settings similar to ours. We however hypothesized that patients with PD would be depressed compared to the control group and the severity of depression will be worse in more advanced PD

METHODS

This cross sectional case-control study was conducted at the Neurology Out-patient Clinic of the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, over a period of 6 months (June–November 2009).

Subjects were recruited using convenience sampling technique. The diagnosis of PD was

based on the United Kingdom (UK) Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [16, 17].

For every patient, we looked for a control with same gender and age +/- 2years. They comprised healthy volunteers without Parkinsonism or significant co-morbidities e.g. hypertension, diabetes mellitus, etc. based on their historical account and physical examination.

Ethical approval to undertake the study was obtained from the UPTH Ethics Committee. Informed written consent was obtained from all recruited subjects.

Sample size estimation

The minimum sample size of patients required for the study was 28, calculated based on the method of Kish [18]. The standard normal deviation (z) was set at 1.96, which correspond to the 95% confidence interval. The proportion of patients with PD (p) was estimated at 59 per 100,000[19], while the absolute deviation from p% that will be tolerated (d) was set at 0.009)

The Beck Depression Inventory^[15]

The Beck Depression Inventory (BDI-II), is a 21-question multiple-choice self-report inventory, one of the most widely used instruments for measuring the severity of depression and the standard by which other depression measures are evaluated[20,21]. It has also been widely used and validated in Nigeria [22, 23]. Its validity and retest reliability in Parkinson's disease has been previously demonstrated [24, 25]. This instrument is more strongly weighted to assess cognitive symptoms of depression (e.g. guilt, loss of pleasure), although it has a number of questions that focus on somatic symptoms. A cluster analysis has shown that the BDI is a valid instrument for quantifying depression in PD patients [26]. The 21-Item BDI-II scale contains 13 items comprising the BDI Cognitive-Affective Subscale which evaluates sadness, pessimism, guilt feeling, irritability, suicidal thoughts and other affective and cognitive symptoms of

depression. The other 8 items that assess sleep disturbance, loss of appetite, fatigue, work difficulty and other somatic and performance decrement make up the BDI Somatic-Performance Subscale [21].

TEST PROCEDURE

Thirty-six consecutive patients who met the inclusion criteria and gave consent as well as thirty six age and sex matched controls were clinically assessed using standardized questionnaires administered by one of the authors (OOC) to obtain demographic information including occupation, marital status, primary language used, medical history, previous psychiatric history, alcohol history and history of use of drugs of abuse. The questionnaire also assessed disease-related variables such as age at onset, duration of disease, duration of treatment, profile of motor and non-motor features of PD. The ease of use of the questionnaire/ proforma for data collection had been pretested in a pilot study using 10 patients and 10 matched controls that satisfied the recruitment criteria. The pilot study was also used to pretest the instrument and proforma before the main study.

On the same day of the clinic visit neurological examination was performed on the patients by a Neurologist (OOC or AGE) to verify the clinical diagnosis of PD. Subsequently, the stage and severity of the disease was determined by using the Hoehn and Yahr staging scale [27] and the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) [28]. Thereafter, all recruited participants were instructed to respond to the BDI items by choosing one of four statements of varying severity that best described the way they had been feeling in the past two weeks including the day of testing. Each item was scored on a four point rating scale with value ranging from 0 (No depression) to 3 (maximum depression). All questionnaires were administered by the authors in English language as all eligible subjects spoke and understood English.

Data Analysis

Summary scores as well as the sub dimensions of BDI were calculated according to its scoring algorithm. Data was analyzed using the SPSS version 15.0. The BDI scores were summarized using means, median and standard deviation. The difference in mean scores between the sample of patients with Parkinson's disease and the reference population were tested using the Students t-test. A p-value of 0.05 or less was considered statistically significant. The association between pattern of scores on subunits of the BDI-II scale and the stage and severity of PD were analysed using t-test and ANOVA/linear regression.

RESULTS

Demographic characteristics

The sample consisted of 36 patients with Parkinson's disease (PD) and 36 healthy controls, comprising 27(75%) men and 9(25%) women in the PD group while the control group consisted of 28(77.8%) men and 8(22.2%) women. The mean age of the patients with PD was 64.3 ± 10.9 years and 63.7 ± 9.2 years for the controls with no significant difference in gender ($p = 0.83$).

More than half of both groups were married (77.8% and 83.3% respectively). Fifteen (41.7%) PD patients as against 24 (66.7%) controls were in paid employment. More than half of the PD patients-21 (58.3%) were retirees. All of the recruited patients and control had no history of previous psychiatric illness or history of consumption of significant quantity of alcohol or of drug of abuse. All patients and controls outside their primary native tongues spoke and understood English language.

Clinical characteristics

Distribution of clinical features among PD patients: Majority of the respondents had motor features. All (100%) had bradykinesia, 34(94.4 %) had tremors while gait abnormalities and imbalance were found in 32(88.9%). Non-motor features most commonly found included persistently low mood in 30(83.3%), pain in 27(75%), olfactory

problems in 27 (75%), and difficulty remembering events in 17(47.2%) and drooling of saliva in 17(47.2%) as shown in Tables 1 & 2.

BDI scores of PD patients compared with Healthy Controls

The mean BDI score for PD patients was 23.6 ± 6.4 with scores ranging from 7 to 36, while that for the controls was 6.2 ± 2.4 , with a range of scores from 0 to 12. There were significant differences in the mean scores of BDI between the PD patients and the controls. ($p \leq 0.001$)

Frequency of Depression among PD patients

Using the cut-off scores empirically established by Kendall et al (1987)[29], only one patient (2.7%) had a BDI score in the range typically considered as non-depressed (0–9), 5.6% in the range considered dysphonic (10–15), and 91.7% in the range frequently labeled as depressed (≥ 16),(Table 3).

Table 4 shows means and standard deviations for each BDI item as well as the prevalence with which each BDI item was positively endorsed (i.e., a non-zero response). Mean ratings for individual items ranged from a low of 0.08 for Item 9 (Suicidal ideation) to a high of 1.86 for Item 20 (Somatic concern). The most frequently endorsed items were depressed mood, decreased initiative, anhedonia and loss of appetite.

Depression and Parkinson disease severity

The BDI scores of PD patients was positively correlated with the UPDRS score ($r = 0.539$ $p = 0.001$). The mean BDI scores of the 29(79.6%) PD patients with Hoehn and Yahr stage 1-3 (classified as moderate PD disease) was 22.45 ± 6.37 while the mean BDI score of the remaining 7(19.4%) patients with Hoehn and Yahr between stage 4 and 5 (classified as severe PD disease) was 28.43 ± 4.83 . This difference in means was statistically significant ($t = 2.32$ $p = 0.027$).

There was however no statistically significant difference between class of depression and Hoehn and Yahr stage of Parkinsonism on chi square test (see table 5).

Table 1: Frequency of motor features among Parkinson's disease patients

Motor feature	Frequency N=36	%
Bradykinesia	36	100.00
Tremor	34	94.40
Gait abnormalities	32	88.90
Imbalance	32	88.90
Rigidity	31	86.10

Table 2: Frequency of non-motor features among Parkinson's disease patients.

Non motor feature	Frequency N=36	%
Persistent low mood	30	83.30
Pain	27	75.00
Olfactory problems	27	75.00
Difficulty remembering event	17	47.20
Drooling saliva	17	47.20
Difficulty falling asleep	12	33.30
Excessive daytime sleepiness	11	30.60
Sweating	10	27.80
Difficulty swallowing	7	19.40

Table 3: Severity of depression using the Beck's Depression Inventory (BDI-II)

Classification	BDI score	No of Patients (%)	No of controls (%)	t	p value
Non depressed	0-9	1(2.70)	30(83.30)		0.101
Dysphonic	10-15	2(5.60)	6(16.70)		4.25
Mild depression	16-20	9(25.00)			
Moderate depression	21-30	18(50.00)			
Severe depression	31-40	6(16.70)			

Table 4: Means, standard deviations, and prevalence of the 21 items on the BDI

BDI ITEM	MEAN ± SD	% Endorsed
1. Depressed mood	1.39 ± 0.84	91.70
2. Pessimism regarding future	0.89 ± 0.75	72.20
3. Sense of failure	0.61 ± 0.90	41.70
4. Anhedonia	1.64 ± 0.96	86.10
5. Guilty feelings	0.69 ± 1.12	33.30
6. Sense of punishment	1.83 ± 1.42	66.70
7. Self-dislike	0.72 ± 0.94	41.70
8. Self-accusation	0.72 ± 0.97	41.70
9. Suicidal ideation	0.08 ± 0.50	2.80
10. Crying	0.97 ± 1.03	58.30
11. Irritability	1.03 ± 1.00	63.90
12. Social withdrawal	0.64 ± 0.88	47.20
13. Difficulty making decisions	0.72 ± 0.88	50.00
14. Distorted body image	0.36 ± 0.68	25.00
15. Decreased initiative	1.97 ± 0.74	97.20
16. Sleep disturbance	1.69 ± 1.12	77.80
17. Anergia/fatigue	0.97 ± 1.11	52.80
18. Loss of appetite	1.40 ± 0.88	80.60
19. Weight loss	1.00 ± 0.96	66.70
20. Somatic concerns	1.86 ± 0.68	69.40
21. Loss of libido	1.67 ± 1.10	77.80

Table 5: Association between BDI classification of depression and stage of Parkinsonism

BDI Classification	H and Y stage		χ^2	p value
	2 and 3	4 and 5		
Non depressed	1	0	6.56	0.161
Dysphonic	2	0		
Mild depression	0	9		
Moderate depression	4	14		
Severe depression	3	3		

DISCUSSION

The frequency of depression among PD patients in this study was very high and significant correlation was found between depression and disease severity. Most Parkinson's disease patients had some form of depression while about half of the population had moderate depression. Estimations of occurrence of depression in patients with

Parkinson's disease vary from 20%-90% according to disease severity and the diagnostic criteria used [30]. A recent study by Ojo et al, reported a high frequency of depression of 55% among forty Parkinson's disease patients in a study in Lagos, Nigeria. This study used the Zung Self Rating Depression Scale [31]. We used the Beck's depression inventory and our overall frequency of 91.7% (mild, moderate and severe) was higher than those from previous studies [30-33]. One reason for this could be that the population for this study was a tertiary care setting. Some investigators have argued that patients with Parkinson's disease in hospital settings are more likely to experience depression than patients with Parkinson's disease who live in the community [1]. Tandberg et al [1], found a lower prevalence rate of 7.7% for major depression using DSM-III criteria, MADRS and BDI scores in a community-based study. While 45% of the patients with Parkinson's disease were found to have mild depression as determined by the MADRS, only 5.1% of these patients were moderately or severely depressed [1].

Our Parkinson's disease patients however showed varied features of depression. The key feature of depression is anhedonia, which is defined as low and an impaired interest or ability to experience pleasure[34]. Our study substantiated this as more than half of the PD patients endorsed anhedonia in the BDI-II. It is good to say here that the profile of depressive symptoms observed in PD is not identical to that reported in patients with idiopathic depression[35]. In this study, we found really elevated levels of decreased initiative, depressed mood (sadness), anhedonia and loss of appetite. We also found high levels of sleep disturbance, loss of libido and pessimism regarding the future but little guilt, self-dislike, sense of failure and very little suicidal ideation. This is similar to the findings of Brown et al [36] who analysed the Beck Depression Inventory scores of 132 patients with PD and found elevated levels of dysphonia and pessimism about the future, irritability, sadness, and suicidal ideation but

little guilt, self-blame, or feelings of failure or punishment. There is however a low suicide rate despite a high frequency of suicidal ideation among patients with PD. This pattern of sadness without guilt or self-reproach has been confirmed by several investigators [37 - 40]

The major difference in our study was the very little suicidal ideation which was the least item endorsed. This difference may not be unrelated to a difference in cultural background. In Nigeria like in most other African countries, most cultures consider suicide a taboo. One other explanation could be the availability of family support from the extended family system that is in operation in Africa. This often mitigates the impact of chronic illnesses on the quality of life of the patient.

Other distinctive features of depression in PD include a high rate of anxiety symptoms, and a relative lack of delusions and hallucinations [7, 32, 41].

These observations indicate that depression in PD is subtly different from idiopathic mood disorders and raises the intriguing possibility that there may be disease-specific depression syndromes with distinctive mood profiles in different conditions. Also in our study, we discovered that depression was worse with severity of Parkinson's disease though depression in Parkinson's disease does not consistently correlate with severity of motor symptoms or functional disability [42 - 44].

A major limitation of this study is the relatively small sample size of recruited patients. This is however a reflection of the rarity of Parkinson's disease. Nonetheless, this study is likely to provide a good representation of clinical practice, in which patients with Parkinson's disease are commonly assessed for depression and treatment instituted early enough to improve their quality of life. Future studies should employ the DSM-IV criteria and other depression scales for comparison.

We therefore conclude that depression is common among patients with Parkinson's disease presenting at the University of Port Harcourt Teaching Hospital. This may also be the case in settings similar to ours in other parts of the Nigeria and sub-Saharan Africa. Treating depression may improve the patient's quality of life. Physicians need to routinely evaluate patients for presence of depression during clinical evaluations.

REFERENCES

1. Tandberg E, Larsen JP, Aarsland D, Cummings JL. The occurrence of depression in Parkinson's disease. A community based study. *Arch Neurology* 1996; 53: 175-179.
2. Reese SL. Psychosocial factors in Parkinson's disease. *Dis Mon.* 2007; 53:291-295.
3. Hemmerle AM, Herman JP, Seroogy KB. Stress, depression and Parkinson's disease. *Exp Neurol.* 2012; 233(1): 79-86
4. Farabaugh AH, Locascio JJ, Yap L, Fava M. Assessing depression and factors possibly associated with depression during the course of Parkinson's disease. *Ann Clin Psychiatry* 2011; 23(3): 171-177.
5. Dobkin RD, Rubino JT, Allen LA, Friedman J, Gara MA, Mark MH, Menza M. Predictors of Treatment Response to Cognitive-Behavioral Therapy for Depression in Parkinson's Disease. *J Consult Clin Psychol.* 2012; 80(4): 694-699
6. Kirsch-Darrow L, Marsiske M, Okun MS, Bauer R, Bowers D. Apathy and Depression: Separate Factors in Parkinson's Disease. *Int Neuropsychol Soc.* 2011; 17(6): 1058-1066.
7. Schiffer RB, Kurlan R, Rubin A, Boer S. Evidence for atypical depression in Parkinson's disease. *Am J Psychiatry* 1988; 145:1020-1022.
8. Cummings JL. Depression and Parkinson's disease: a review. *Am J Psychiatry* 1992; 149:443 - 454.
9. McDonald WM, Richard IH, DeLong MR. Prevalence, etiology and treatment of

- Depression in Parkinson's disease. *Biol Psychiatry* 2003; 54:363-375.
10. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in PD. *Parkinsonism and Related Disorders* 2002; 8:193-197
 11. Allain H, Schuck S, Mauduit N. Depression in Parkinson's disease. *BMJ* 2000; 320:1287-1288.
 12. Liu CY, Wang SJ, Fuh JL, Lin CH, Yang YY, Liu HC. The correlation of depression with functional activity in Parkinson's disease. *J Neurol* 1997; 244:493-498.
 13. The Global Parkinson's Disease Survey (GPDS) Steering Committee. Factors Impacting on QOL in PD: Results from an International survey. *Mov Dis* 2002; 17:60-67.
 14. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring Depression. *Arch Gen.Psychiatry* 1961; 4: 561-571.
 15. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of Clinical diagnosis of idiopathic Parkinson's disease. A Clinico-pathological study of 100 cases. *J NeurolNeurosurg Psychiatry* 1992; 55 (3): 181 – 184.
 16. Bhatia KP, Burn DJ, Goetz CG, Lang AE, Mckeith I, Quinn N, et al; Movement Disorder Society Scientific Issues Committee. Movement Disorder Society Scientific Issues Committee report: SIC Task force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Dis.* 2003; 18: 467 – 486.
 17. Leentjens AF, Verhey FR, Luijckx GJ, Troost J. The Validity of the BDI as a screening and diagnostic instrument for depression in patients with Parkinson's disease. *Mov Dis.* 2000; 15:1221-1224.
 18. Kish L. Survey sampling. New York: John Wiley and Sons; 1965.
 19. Schonberg BS, Osuntokun BO, Adeuja AOG, Bademosi O, Nottidge V, Anderson DW, et al. Comparison of the prevalence of Parkinson's disease in black populations in the rural United States and in rural Nigeria: Door-to-door community studies. *Neurology* 1988; 38: 645-46.
 20. Spielberger CD, Ritterband LM, Reheiser EC, Brunner TM. The nature and measurement of depression. *Int. J Clinical and Health Psychology* 2003; 3(2): 209-234.
 21. Adewuya AO, Ola BA, Aloba OO. Prevalence of major depressive disorders and validation of the Beck Depression Inventory among Nigerian adolescents. *European Child Adolescent Psychiatry* 2007; 16(5): 287-292.
 22. Dozois DJA, Dobson KS, Ahnberg JL. A psychometric evaluation of the Beck Depression Inventory-II. *Psychological Assessment* 1998; 10(2): 83-89.
 23. Ikem RT, Ikem IC, Ola BA. Relationship between depression, cognitive function and quality of life of Nigerians with diabetic foot ulcers. A preliminary controlled study. *ActaEndocrinologica(Buc)* 2009; 1: 75-83.
 24. Visser M, Leentjens AF, Marinus J, Stiggelbout AM, van Hilten JJ. Reliability and validity of the Becks Depression Inventory in patients with Parkinson's disease. *Mov Dis.* 2006; 21: 668-672.
 25. Kuhner C, Burger C, Keller F, Hautzinger M. Reliability and validity of the revised Beck Depression Inventory (BDI-II). Results from German sample. *Nervenarzt* 2007; 78(6): 651-656.
 26. Levin BE, Llabre MM, Weiner WJ. Parkinson's disease D and Depression: psychometric properties of the BDI. *J NeurolNeurosurg Psychiatry* 1988; 51:1401-1404.
 27. Hoehn MM and Yahr MD. Parkinsonism: onset, progression and mortality. *J. Neurology* 1967; 17: 427-442.
 28. Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): process, format, and clinimetric testing plan. *MovDisord* 2007; 22:41-47

29. Kendall PC, Hollon SD, Beck AT, Hammen CL, Ingram RE. Issues and recommendations regarding the use of the Beck Depression Inventory. *Cognitive Therapy and Research*. 1987; 11:289–299.
30. Leentjens AF. Depression in Parkinson's disease: conceptual issues and clinical challenges. *J Geriatric Psychiatry Neurol* 2004; 17:1200-1206.
31. Ojo OO, Okubadejo NU, Ojini FI, DeMA. Frequency of cognitive impairment and depression in Parkinson's disease: A preliminary case-control study. *Niger Med J* 2012; 53(2): 65-70.
32. Ceravolo NA, Ceravolo R, Picinni A. Psychiatric comorbidity in a population of Parkinson's disease patients. *Eur J Neurol* 2004; 11:315-320.
33. ZiropadjaLj, Stefanova E, Petrovic M, Stojkovic T, Kostic VS. Apathy and depression in Parkinson's disease: the Belgrade Parkinson's disease study report. *Parkinsonism Relat Disord*.2012; 18(4): 339-42.
34. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 3rd ed. Washington, DC: American Psychiatric Association, 1980.
35. StarksteinSE, MerelloM, JorgeR, Brockman S, Bruce DG, Petracca G, Robinson RG. A validation study of depressive syndromes in Parkinson's disease. *MovDisord*2008; 23: 538–46.
36. Cummings JL. Depression and Parkinson's disease: a review *Am J Psychiatry* 1992; 149:443–454.
37. Brown RG, MacCarthy B, Gotham AM, Der GJ, Marsden CD. Depression and disability in Parkinson's disease: a follow up study of 132 cases. *Psychol Med* 1988; 18:49-55.
38. Taylor AE, Saint-Cyr JA, Lang AE, Kenny FT. PD and Depression: a critical re-evaluation. *Brain* 1986; 109:279-292.
39. Levin BE, Llabre MM, Weiner WJ. Parkinson's disease and depression: psychometric properties of the BDI. *J NeurolNeurosurg Psychiatry* 1988; 51:1401-1404.
40. Huber SJ, Friedenberg DL, Paulson GW, Shuttleworth EC, Christy JA. The pattern of depressive symptoms varies with progression of Parkinson's disease. *J NeurolNeurosurg Psychiatry* 1990; 53:275-278.
41. Gotham AM, Brown RG, Marsden CD: Depression in Parkinson's disease: a quantitative and qualitative analysis. *J NeurolNeurosurg Psychiatry* 1986; 49:381-389.
42. Brown GL, Wilson WP. Parkinsonism and depression. *South Med Jour* 1972; 65: 540-545
43. Mindham RHS, Marsden CD, Parkes JD. Psychiatric symptoms during L-dopa therapy for Parkinson's disease and their relationship to physical disability. *Psychol Med* 1976; 6: 23-33.
44. van der Hoek TC, Bus BA, Matui P, van der Marck MA, Esselink RA, Tendolkar I. Prevalence of depression in Parkinson's disease: effects of disease stage, motor subtype and gender. *J Neurol Sci*.2011; 310(1-2):220-224