Clinical examination of non-motor symptoms in Parkinson's Disease

PhD Thesis

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2. ABBREVIATIONS

ACE	Addenbrooke Cognitive Examination
AUC	Area under curve
BDI	Beck Depression Inventory
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
EQ-5D	EuroQol 5D Instrument
EQ-VAS	Az ED-5D Visual Analogue Scale
ESS	Epworth Sleepiness Scale
HAM-A	Hamilton Anxiety Scale
HYS	Hoehn-Yahr Scale, Hoehn-Yahr Stage
HRQoL	Health-Related Quality of Life
ICD	Impulse control disorders
LARS	Lille Apathy Rating Scale
MADRS	Montgomery-Asberg Depression Rating Scale
MC	Motor complications (MDS-UPDRS part IV.)
MDRS	Mattis Dementia Rating Scale
MDS	Movement Disorders Society
MDS-UPDRS	Movement Disorders Society–sponsored Unified Parkinson's Disease Rating Scale
ME	Motor Examination (MDS-UPDRS part III.)
M-EDL	Motor Experiences of Daily Living (MDS-UPDRS part II.)
mHYS	Modified Hoehn-Yahr Scale
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
nM-EDL	Non-motor Experiences of Daily Living (MDS-UPDRS part I.)
NMS	Non-motor symptoms
NMSS	Non-Motor Symptoms Scale
PDQ-8	Parkinson's Disease Questionnaire -8 items version
PDQ-39	Parkinson's Disease Questionnaire – 39 items version
PDQ-39 SI	Parkinson's Disease Questionnaire– 39 items version Summary Index
PDQL	Parkinson's Disease Quality of Life Questionnaire
PDSS	Parkinson's Disease Sleep Scale
PDSS-2	Parkinson's Disease Sleep Scale 2nd version
PK	Parkinson's Disease
PK-ICD	Patients with Parkinson's disease and impulse control disorders
QUIP	Questionnaire for impulsive-compulsive disorders in Parkinson's disease

ROC	Receiver operating characteristic
SD	Standard deviation
SEM	Standard error of measurement
SES	Schwab-England Scale
SF-36	Short-form 36 Health Survey
SPECT	Single-photon emission computed tomography
VAS	Visual Analogue Scale
UDysRS	Unified Dyskinesia Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale

3. INTRODUCTION

The first description of four basic symptoms of Parkinson's disease (bradykinesia, tremor, rigidity, and postural instability) can be related to Ferenc Pápai-Pariz [1]. However, the disease became well-known to the medical community 127 years later, after James Parkinson published his famous paper in 1817 [2].

Parkinson's disease is considered to be the second most common neurodegenerative disease after Alzheimer's disease [3]. There is no clear answer to the question of why PK develops. In a pathological viewpoint, PK is characterized mainly by the damage to dopamine-producing cells in the substantia nigra and the presence of α-synuclein-containing Lewy bodies in certain regions of the nervous system. In addition, the damage of the noradrenergic and cholinergic neurotransmitter systems can be also responsible for the extremely complex symptomology of PD. [3].

3.1. CLINICAL STAGES OF PARKINSON'S DESEASE

At the onset of the first symptoms of Parkinson's disease, the death of a significant proportion of the dopamine-producing cells in the substantia nigra is already assumable. This also implies the existence of a preclinical state which can be last for years *(Figure 3.1).*

The progress of Parkinson's disease can be divided into different clinical stages according to the classification updated in 2014 [9], as shown in Figure 3.1

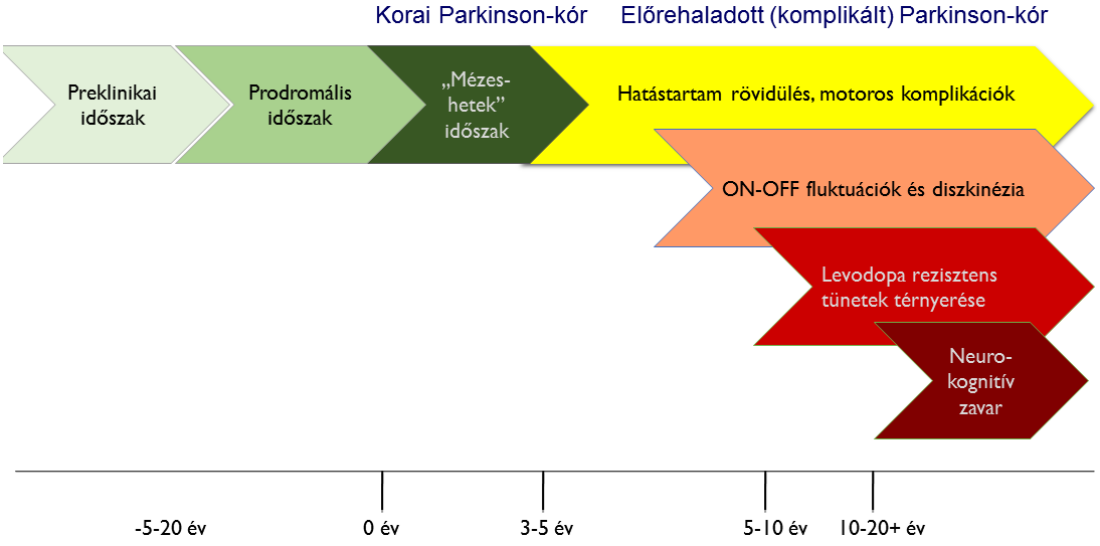

Figure 3.1. The clinical stages of PD

3.2. DIAGNOSIS OF PARKINSON'S DISEASE

At present, the diagnosis of PK can only be made by histological examination. However, careful analysis of the clinical symptoms can allow us to make the clinical diagnosis with sufficient accuracy. In clinical trials, the diagnosis is mainly based on the UK Brain Bank Diagnostic Criteria [14, 15]. New clinical criteria system of Movement Disorders Society (MDS)

available since 2015 [7], however, clinicopathological confirmation of it is still ongoing, so in my clinical research, the UK Brain Bank Criteria System was used [14, 16].

3.3. SYMPTOMS OF PARKINSON'S DISEASE

3.3.1. Motor symptoms

The starting point for clinical diagnosis is the appearance and detection of motor symptoms. **(Table 3.2**)

Table 3.2. The major symptoms of Parkinson's Disease

Motor (movement related) symptoms	Non-motor symptoms

• bradykinesia (a combination of slowness and motion with decreasing amplitude and / or speed)
• rigidity (a type of muscle tone enhancement where agonist and antagonist muscle tones are abnormally increased)
• tremor
 	
Symptoms of advanced stage of the disease:
• Postural instability
• Motor complicatons
  ○ Medication duration shortened
  ○ ON-OFF fluctuation
  ○ Biphasic dyskinesia
  ○ Dystonia
  ○ Delayed ON
  ○ No ON phenomenon
	Early-stage symptoms
	• Nausea
	• Constipation
	• Hyposmia
	• Depressive mood
	• Apathy
	• Anxiety
	• Sleeping disorders
	• Daytime sleepiness
	• Fatigue
	• Pain
	• Difficulty in concentration
	
	Symptoms of advanced stage of the disease:
	• Urinary problems
	• Erectile dysfunction
	• Sexual disfunction
	• Salivation
	• Increased sweating
	• Orthostatic hypotension
	• Hallucinations
	• Neurocognitive disorders

List of the most common and important motor and non-motor symptoms of Parkinson's disease. By dyskinesia is meant choreiform hyperkinesia and dystonia [17].

As the disease progresses, the effectiveness of the medication will be reduced (wearing off), along with alternating periods of good and bad movement performance (ON-OFF

fluctuation). Unintentional hypermobility or abnormal posture may also occur (dyskinesia and dystonia).

3.3.2. Non-motor symptoms

Possible changes in dopamine level play an important role not only in the performance of various movements, but also in a variety of non-motor areas such as pleasure, motivation, mood control, rewarding and development of addiction. All of these provide a significant basis for the diversity of symptoms of Parkinson's disease [18]. In addition, certain problems that occur during illness can severely impair patients' ability to work, such as sleep disorders, abnormal fatigue, and reduced ability to concentrate. Cognitive disorders, urinary problems, and increased salivation in the more severe stages of PK may also have serious consequences for the quality of life of PK patients.

In some cases, non-motor symptom variability limits patients' health-related quality of life (HRQoL) more than motor symptoms.

4. OBJECTIVES

In the clinical examination of the non-motor symptoms of Parkinson's disease, I set the following objectives:

1. In a large cross-sectional study, the incidence and severity of non-motor symptoms in Hungarian patients with Parkinson's disease were assessed. In addition to the epidemiological survey, the further aim of my study was to clarify the role of female sex in quality of life, which is currently controversial in the literature. (Chapter 5.)
2. Validation of the Hungarian, self-completed version of the Parkinson's Anxiety Scale, and examination of the basic clinimetric features of the questionnaire. (Chapter 6.)
3. Assessing the incidence and severity of anxiety among Hungarian PD patients in a large sample sized clinical trial. (Chapter 6.)
4. Examination of relationship between impulse control disorders and Internet use and Internet addiction in Parkinson's disease. (Chapter 7.)

I discuss all of the clinical studies in separate chapters, as the patient populations I studied and the methods I used differ significantly.

5. EXAMINATION OF NON-MOTOR SYMPTOMS IN PARKINSON'S DISEASE

Recently the nonmotor symptoms (NMS) of Parkinson's disease (PD) have been increasingly recognized as a major burden of the health-related quality of life (HRQoL) [20, 21]. There are also NMS symptoms in Parkinson's disease that occur as a side effect of medication, such as impulse control disorders (ICD) or psychosis. The importance of non-motor symptoms is further enhanced by the finding that health-related quality of life (HRQoL) is often more severe than motor symptoms.[22, 33].

The effect of female sex on the onset of PK symptoms has been confirmed by several studies, including that there may be differences in the appearance patterns of motor and non-motor symptoms by sex. However, when we examine the health-related quality of life, the effect of the female sex is not sufficiently clarified. A large number of studies argue that female sex, as an independent factor, may be a predictor of poorer quality of life, but other studies suggest that this phenomenon is due to sex-specific non-motor symptomology.

5.1. OBJECTIVE

With the help of my team, we have evaluated the incidence and severity of non-motor symptoms in patients with Parkinson's disease using a large sample size cross-sectional study. This has not been studied systematically in Hungarian PK patients with this large sample size. In addition, we wondered if female sex is able to independently influence health-related quality of life also independently of other non-motor symptoms in Parkinson's disease.

5.2. METHODS

5.2.1. Patients

In our cross-sectional study 621 Parkinson's patients took part, they were all treated at the Neurological Clinic of the University of Pécs, patients were diagnosed according to the UK Brain Bank Criteria System [14].

5.2.2. Assessment of motor symptoms

The severity of Parkinson's disease symptoms was assessed by the Hungarian version of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [40, 41] and the Hoehn-Yahr Scale (HYS) [42]

5.2.3. Assessment of non-motor symptoms and quality of life

To get a global view of non-motor symptoms, we used the Non-Motor Symptoms Scale (NMSS) and the MDS-UPDRS Scale [40, 41, 47].

Presence and severity of sleep disturbances were specifically measured by the Hungarian validated version of PDSS-2 [48-50], In the meantime, daytime sleepiness was assessed by the Epworth Sleepiness Scale [51, 52]. Depression, anxiety, and apathy were assessed by the Hungarian validated versions of the Montgomery Depression Scale (MADRS), the Hamilton Anxiety Scale (HAM-A) [53], and the Lille Apathy Scale (LARS) [54]. Cognitive performance was examined by the Hungarian validated versions of Mini-Mental Status Examination (MMSE,) Addenbrooke Cognitive Examination (ACE) [55], Mattis Dementia Rating Scale (MDRS) [55], and Montreal Cognitive Assessment (MoCA) [56]. Presence and severity of impulse control disorders (ICD) were assessed by the questionnaire for impulsive-compulsive disorders in Parkinson's disease (QUIP) Health-related quality of life (HRQoL) was measured by the Hungarian validated version of the disease-specific PDQ- 39 Summary Index (PDQ-39 SI) [59] and the nondisease specific EuroQol instrument (EQ-5D index value) [60].

5.2.4. Statistical analysis

All statistical analyses were carried out using the IBMSPSS software package (version 22.0.1, IBM Inc., Armonk,NY, USA).: Because data from these scales followed the normal distribution,mean and standard deviations (SD) were calculated. For group comparisons, independent samples *t*-tests were applied. For categorical variables (e.g.,having or not having a symptom) Chi-square tests were used. A multiple regression modelling using a stepwise method was initiated to predict the PDQ-39 SI from various clinical variables. Subsequently, another multiple regression analysis was performed to predict the EQ-5D index values from the same variables using a stepwise method.

5.3. RESULTS

5.3.1. Demographic data

The subject population consisted of 621 consecutive PD patients (361 males, age: 66.9 ± 9.2 years, disease duration: 7.6 ± 6.1 years). Two-hundred and forty-seven patients had rigid-akinetic, 194 had tremor dominant, and 180 had mixed type of PD.

5.3.2. Motor symptoms of PD

Although age at PD onset, disease duration, education years, and severity of motor symptoms (MDS-UPDRS ME) were comparable between the males and females, men received significantly higher dosage of antiparkinson medication (725,8 ± 594,8 mg vs. 584,7 ± 424,5 mg, p=0,001).

Based on the M-EDL MDS-UPDRS, the overall motor symptoms were associated with similar disabilities in both sexes. Although the axial scores on MDS-UPDRS ME were comparable, females had significantly worse postural instability (item 3.12) and gaitrelated disabilities (item 2.12).

In the examined population, 39.9% of males and 34.6% of females had fluctuations (p = 0.181, Chi-square test). Despite of receiving less dopaminergic medication, women had significantly worse dyskinesia compared to men (UDysRS total score: 35.5 ± 18.6 versus 30.1

± 17.4 points, resp., p = 0.006). However, the analysis of the patient diaries revealed that both sexes had comparable ON and OFF time. The only statistically significant difference was the time of daytime sleep (males: 0.7±1.2 hours versus females: 0.5±0.8 hours, p = 0.005).

5.3.3. Non-motor symptoms of PD

Based on the 13 screening items of nM-EDL part of MDS-UPDRS, our patientshad an averageof 8.08±2.78 NMSsymptoms. Female patients had more severe nonmotor symptoms in general. This finding is congruently supported by the nM-EDL part of MDS-UPDRS (15.1 ± 7.9 versus 13.8 ± 7.5 points, p = 0.034) and NMSS scores (64.1 ± 41.1 versus 57.4 ± 41.2 points, p = 0.045).

Among female PD patients the anxiety was not only significantly more frequent (85.0% versus 76.5%, p = 0.005),but also more severe (HAM-Ascore: 16.0± 6.9 versus 12.5 ± 6.0, p = 0.001). Although the prevalence of depression was comparable between both sexes (76.2% versus 73.7%, p = 0.386), the severity of depression was worse in women (MADRS score: 14.2±7.6 versus 11.8±8.0, p = 0.003). Similarly, the "Mood problems" section of NMSS demonstrated more severe affective problems in the female individuals (15.3±12.3 versus 12.4±14.3, p = 0.016).

Based on the Hungarian validated threshold values for PDSS-2, 72.7% of females and 63.4% of males reported sleep-related problems (p = 0.034). Although the female PD patients had more severe nighttime sleep disturbances (measured by the total score of PDSS-2), daytime sleepiness was more common (39.3% versus 26.9%, p = 0.001) and more severe among males.

Based on the screening item of MDS-UPDRS (1.12 orthostatic symptoms) and the "Cardiovascular" section of NMSS, female patients had more often (71.5% versus 62.6%, p = 0.023) and more severe problems than males (3,8 ± 4,1 vs. 2,9 ± 3,8 points p = 0.004).

Based on the screening item of MDS-UPDRS (1.9 Pain) and the item 27 of NMSS (Pain), women had more frequent (76.5% versus 67.3%, p = 0.014) and more severe (4.8 ± 3.7 versus 2.1 ± 3.1, p < 0.001) pain sensations than men.

Male patients had more frequent (31.6% versus 18.1%, p < 0.001, Chi-square test) and more severe sexual problems than females (2.9±5.8 versus 1.8±5.2, p = 0.022).

Although the prevalence of apathy was comparable (18.5% versus 21.9%, p = 0.279), males had more severe apathetic symptoms measured by LARS than females (−20.4 ± 10.8 versus −22.8 ± 8.9, p = 0.004).

No statistically significant differences were found between the sexes in the following symptoms: Neurocognitive symptoms (MMSE, ACE, MoCA, MDRS), urinary, gastrointestinal and hallucinatory problems and fatigue.

5.3.4. Impulse control disorders in PD

Based on the analysis of QUIP, 21.6% of male and 20.0% of female PD patients had any type and any degree of ICD problems (p = 0.850). The prevalence and severity of pathological gambling, compulsive eating, and punding were similar in both sexes. However, men had more

often hypersexuality (5% versus 0%, p < 0.001) and women had more frequent and severe compulsive buying (18.5% versus 6.4%, p < 0.001).

5.3.5. Health-related quality of life

Although both male and female PD patients had similar everyday functioning measured by the SES (75.0 ± 16.2 versus 74.1 ± 19.4 points, p = 0.636), female patients had worse HRQoL than males (EQ-5D index value: 0.620 ± 0.240 versus 0.663 ± 0.229, p = 0.026 and PDQ-39 SI: 27.1 ± 17.0 versus 23.5 ± 15.9, p = 0.010).

5.3.6. Determinants of HRQoL in PD

Multiple regression analysis was performed to estimate the PDQ-39 SI based on various clinical factors. Using a stepwise method it was found that M-EDL part of MDS-UPDRS (importance = 0,53; β = 0.883, p < 0.001), PDSS-2 total score (importance = 0.12; β = 0.260, p < 0.001), MADRS total score (importance = 0.09; β = 0.423, p = 0.002), sex (coded as 1 = males and 2 = females, importance = 0.06; β = −3.389, p = 0.010), ME part of MDS UPDRS (importance = 0,05; β = −0.134, p = 0.012), SES (importance = 0.04; β = −0.124, p = 0.017), UDysRS total score (importance = 0.03; β = 0.166, p = 0.013), HAM-A total score (importance = 0.03; β = 0.258, p = 0.019), ACE total score (importance = 0.03; β = −0.118, p = 0.027), QUIP total score (importance = 0.02; β = 0.667, p = 0.029), and ESS total score (importance = 0.02; β = 0.186, p = 0.038) explain the highest significant amount of variance in the value of the PDQ-SI score (intercept = 22.433, F(9, 593) = 120.400, p < 0.001, $R2$ adjusted = 0.741). The other examined variables did not significantly contribute to the model.

For estimating the EQ-5D index value SES (importance = 0.47; β = 0.006, p < 0.001), M-EDL part of MDSUPDRS (importance = 0.33; β = −0.010, p < 0.001), PDSS-2 total score (importance = 0.11; β = −0.004, p = 0.013), ME part of MDS-UPDRS (importance = 0.04; β = −0.002, p = 0.012), UDysRS total score (importance = 0.03; β = −0.162, p = 0.016), QUIP total score (importance = 0.03; β = −0.011, p = 0.018), MADRS total score (importance = 0.02; β = −0.002, p = 0.038), and sex (coded as 1 = males and 2 = females, importance = 0.04; β = 0.032, p = 0.010) contributed significantly to a model (intercept = 0.318, F(4, 309) = 46, 547, p < 0.001, $R2$ adjusted = 0.608).

5.4. DISCUSSION

5.4.1. Motor symptoms and motor complications

First, we were unable to detect any sex-related differences in the major demographic data (e.g., age at disease onset, disease duration, and education level) and overall motor performance. Although females received significantly lower dose of levodopa, the severity of motor symptoms (MDS-UPDRS ME) and the disability related to motor symptoms (MDSUPDRSM-EDL) were comparable between both sexes. Despite of the lower overall levodopa dosage, women had worse dyskinesia measured by UDysRS.

Because previous studies demonstrated that female sex is associated with significantly worse postural instability and more frequent falls [66-68], therefore, we separately analyzed

items 3.12 “Postural instability” and 2.12 “Walking and balance” of MDS-UPDRS. In these two items, women had significantly worse. The other items of MDS-UPDRS M-EDL and ME did not differ between man and women (data not shown).

5.4.2. Non-motor symptoms

Based on our data, more than 99% of the patients had at least one NMS with an average number of 8 out of the 13 items screened by theMDS-UPDRS. The most prevalent NMS problems were fatigue, anxiety, depression, daytime sleepiness, and pain. These findings are congruent with the literature [70, 71].

Consistent with the previously published data, we demonstrated that anxiety [23, 34, 35], pain [23, 35, 36], nocturnal sleep difficulties, and orthostatic symptoms were more frequent among female PD patients while the prevalence of sexual dysfunction[23, 38, 39, 72] and daytime sleepiness were more common among males [23, 73]. Although depression was similarly common among both sexes [25], the depressive symptoms were more severe in females [74, 75]. Contrarily, the apathetic symptoms were more pronounced in males despite of their similar occurrence in both sexes. In our cohort, we could not find any sex-related differences in the frequency and severity of fatigue. This result is partly contradictory to previous research data [23, 63, 76, 77].

We did not find significant differences in the prevalence of global ICD symptoms between both sexes. Though total ICD frequency was similar for men and women, there were notable sex differences in the frequency of specific ICDs, with hypersexuality more common in males and compulsive buying and binge eating were more prevalent in women. These sex-related differences were previously reported [82].

5.4.3. Determinants of HRQoL in PD

The role of sex on HRQoL in PD is highly controversial. In more detail, we can divide the currently available results into four categories: (1) In some previous studies, no relationship was observed between female sex and quality of life [83-91, 22]. (2) Studies have also been published that have not statistically evaluated the influence of sex as an independent factor on quality of life. [92-94, 20]. (3) Some of the studies published so far have shown sex differences in the quality of life of Parkinson's patients, but have failed to confirm the role of the female gender in this. [95, 96] (4) However, there have been many studies that have shown that female sex is adversely affect the quality of life of Parkinson's patients [97-104].

Based on the above, it is likely that methodological and sociocultural reasons may be behind some of the varied, often conflicting results. The present study has shown that feale sex is able to induce different motor and non-motor symptoms, but as an independent factor, it can negatively influence quality of life.

It is likely that the sex differences in the symptoms of Parkinson's disease may be due to the complex mechanism of action of estrogen. Due to its complex mechanisms, estrogen can influence neurotransmission, dopamine reuptake, production, and excretion. [105]. Animal studies suggest that estrogen may be able to prevent damage to certain neurons [106],

and possibly because of this, a higher incidence of PK can be identified in men. In addition, estrogen may also play a role in increasing the bioavailability of levodopa [107], this may explain the more severe dyskinesia in female PK patients, even with lower dopaminergic medication [108].

5.4.4. Limits of the study

However, many factors may limit the evaluation of the results obtained, in particular the monocentric nature of the study and the differences between the tests we use and those used in the previous studies.

5.5. CONCLUSIONS

For the first time in Hungary, the incidence and severity of motor and non-motor symptoms in Parkinson's disease were assessed using a large cross-sectional study. Our results show that 99.1% of patients have some non-motor symptoms, as well as non-motor symptoms and motor complications more severely in women than in men.

Multivariate stepwise regression analysis has shown that female sex may be independent predictors of quality of life in Parkinson's disease, independently from non-motor symptoms. Based on previous studies and our own results, it can be assumed that socio-cultural differences, different patient samples, and the use of different test batteries may be behind the often contradictory studies on the effects of female gender.

6. EXAMINATION OF ANXIETY IN PARKINSON'S DISEASE

6.1. INDRODUCITON

One of the most important non-motor symptoms of Parkinson's disease (PK) is affective problemsAccording to epidemiological studies, anxiety disorders are more common than depression, with an incidence of 25-49% Along with the feeling of suffering, anxiety has a serious impact on everyday life and health-related quality of life (HRQoL) [89].

The Parkinson Anxiety Scale (PAS) is a 12-item tool which can be either rated by a trained professional (observer version) or by the patients themselves (patient-rated version). The PAS make up three different subscales describing the persistent anxiety (5 items), episodic anxiety (4 items), and avoidance behavior (3 items) [114]. Each item can be scored on a 5-point Likert scale, with "0" meaning "not or never" and "4" meaning "severe or almost always" implying a maximum of total score of 48 points. Based on a multinational, multicenter, and cross-sectional validation study enrolling 360 PD patients, the PAS had better clinimetric properties than any other existing scale making it a brief and nevertheless valid and highly reliable tool. The aim of this study to validate Hungarian version of PAS scale for determining the prevalence and severity of anxiety in a large pool of Hungarian subjects with PD in a cross-sectional study.

6.2. MATERIALS AND METHODS

6.2.1. Patients

While in the validation part of the study, 190 consecutive patients fulfilling the clinical criteria for PD were enrolled, another 590 PD subjects participated in the subsequent part assessing the prevalence of anxiety. Besides recording demographic data disease-specific data were also noted.

6.2.2. Validation of the Hungarian Parkinson Anxiety Scale

Two native Hungarian speakers fluent in English translated independently the PAS into Hungarian, and an English speaking psychologist back-translated the PAS into English. Subsequently, the original and the back-translated versions were compared and any discrepancies were fixed to achieve the first Hungarian patient-rated and observer-rated PAS. Cognitive debriefing was applied on 25 patients before field testing.

6.2.2.1. Neurological and neuropsychological assessments

The severity of PD-related symptoms was globally assessed by the Hungarian-validated version of the MDS-UPDRS [69, 118]. As a part of the MDS-UPDRS, the Hoehn and Yahr Scale (HYS) was also taken to detect the overall severity of PD. Disease severity was

categorized as mild (HYS 1 and 2), moderate (HYS 3), and severe (HYS 4 and 5) [119, 120].

The nM-EDL part of the MDS-UPDRS has items evaluating the presence and severity of 13 NMS including depression and anxiety [69]. To assess nonmotor symptoms globally, the Nonmotor Symptoms Scale (NMSS) was also included [122, 123]. Severity of depression was assessed by the Hungarian-validated versions of the Montgomery Depression Scale (MADRS) [124] whereas, the severity of anxiety was measured by the Hamilton Anxiety Scale (HAM-A) [53] and the PAS, and apathy was rated by the Lille Apathy Rating Scale (LARS) [125].

Patients were screened for the presence of mild and major neurocognitive disorders by validated neurocognitive tests[126] (Montreal Cognitive Assessment, cutoff scores <23.5 and <20.5, respectively, and Mattis Dementia Rating Scale, cutoff scores <139.5 and <132.5 points, resp.) [127, 128]. Health-related quality of life (HRQoL) was measured by the Hungarian-validated version of the disease-specific PDQ-39 Summary Index (PDQ-39 SI) [129, 130]. Subsequently, the presence of anxiety in accordance with the DSM-5 criteria [117] was assessed by a trained neuropsychiatrist in the validation phase.

6.2.2.2. Statistical analysis

Statistical Analysis. For variables following the normal distribution (e.g., age, disease duration), means ± standard deviations (SD) were calculated. Data quality was defined as the proportion of computable data. The criterion for an acceptable amount of missing data is <10% [131]. For acceptability, the floor and ceiling effect should be kept <15% [132], and the skewness should range between −1 and +1 [133].

Before the structure of the scale was explored by a factor analysis, the value of Kaiser-Meyer-Olkin measure of sampling accuracy (KMO) was calculated. A KMO >0.60 is a minimum requirement; whereas, KMOs >0.90 are considered as excellent for factor analysis. We accepted only those factors having an eigen value >1 and a Scree test for factor analysis. In our study, the internal consistency was evaluated by four different approaches [135]: (1) Cronbach's α should be >0.70 [136]. (2) Corrected item-total correlation should be >0.30 for each item. (3) Item homogeneity coefficient should be >0.30 (4) Test-retest properties (Intraclass Correlation Coefficient, ICC should be >0.6) [49]. The retest properties of the PAS were analyzed on a subset of patients (n = 89) one day after the initial examination.

The validity of our study was based on three different methods:

- Convergent validity: The total score and the subscores of PAS were compared to the "Anxiety" item of MDS-UPDRS and HAM-A. For correlation, Spearman's rank correlation coefficients were calculated.
- Internal validity: the correlation between the domains (subscales) should not be too low (rS< 0.300) or too high (rS> 0.700) either [138].
- Divergent validity: We tested the discriminative validity of the PAS against

apathy (Lille Apathy Rating Scale), depressive syndromes (BDI and MADRS), and cognitive functioning (MoCA) by calculating Spearman rank correlation coefficients [114].

The precision of the PAS was estimated by the standard error of measurement (SEM), where the value of SEM should be less than the half of the standard deviation.

In order to establish a cutoff value for the total score of the PAS, which can reliably differentiate PD patients with and without anxiety, we applied receiver operating curve (ROC) analysis. Patients were categorized by the DSM-5 criteria for anxiety disorders. This categorization served as the state variable and the PAS total score as the test variable. The best cutoff value was estimated as the point on the ROC curve closest to the point of (0.1). Besides, the area under the curve, specificity, sensitivity, and positive and negative likelihood ratios were calculated for the best cutoff value. After establishing the optimal threshold for the whole population, separate cutoff limits were calculated for the different disease severity categories.

All statistical analyses were carried out using IBM SPSS software package (version 24.0.0.1, IBM Inc., Chicago, USA). Statistical significance level was set to 5%.

6.2.3. Determining the frequency of anxiety in Hungarian patients with Parkinson's disease

Using newly established cutoff score for anxiety, screening was performed on a large number of Parkinson's patients (n=590). The presence and severity of anxiety was assessed by the patient-rated version of PAS.

6.3. RESULTS

6.3.1. The validation of Hunagarian Parkinson Anxiety Scale

The subject population consisted of 190 PD patients without major neurocognitive disorder.

The KMO value was sufficiently high (0.909) to enable a factor analysis. The Scree test supported a three-factor solution explaining 67.6% of the variance. Using the Principal Component Analysis extraction method with Promax rotation, we identified the same factor structure as it was originally described.

The value of Cronbach's α for the total score and the persistent, episodic, and avoidance domains was acceptable (0.935, 0.897, 0.828, and 0.724, resp.). All the items reached the 0.30 threshold value for the item-total correlation. Item homogeneity index values were acceptable for all subdomains and the total score of PAS. The total score of PAS demonstrated high Spearman's rank correlation coefficient with both HAM-A and MDS-UPDRS "Anxiety" item (0.618 and 0.602). The internal validity for the subdomains of PAS was acceptable (rS values in the range of 0.300–0.700). The test-retest validity was also acceptable (ICC = 0.824). As far as the discriminative properties were considered, the total

score of PAS had poor correlation with LARS (rho = 0.226, p < 0 05), MoCA (rho = −0.185, p < 0 05), and moderate correlation with depression (MADRS rho = 0.536, p < 0 05, and BDI rho = 0.586, p < 0 05, overall population). In patients without anxiety, the rho values were 0.219 and 0.317 for MADRS and BDI; whereas, in the presence of anxiety, these values increased to 0.504 and 0.584, respectively. These discriminant values were similar to those of the original PAS validation study [114] and the Italian language validation study [115]. The precision was acceptable for both the domains and the total score of PAS. Based on the DSM-5 criteria, 78 patients (41.1%) had an anxiety disorder. Generalized anxiety was found in 52 (27.3%), agoraphobia and social phobia in 48 patients (25.3%), and panic disorder in 31 patients (16.3%).

The cutoff value for PAS which best discriminated the presence of anxiety from the absence was 12.5 points. Therefore a PAS score ≥ 13 points may suggest the presence of anxiety (sensitivity of 88.6%, specificity of 79.9%, positive likelihood ratio: 2.64, and negative likelihood ratio: 0.17). The area under the curve (AUC) was 0.847 whereas the ROC analysis yielded the statistical significance level (p < 0 001). The optimal threshold values for mild, moderate, and severe disease stages were slightly different (10.5, 12.5, and 13.5 points, resp.). Subsequently, we also calculated the most optimal threshold values for each subscale **(Table 6.2)**.

Table 6.2. Calculation of the optimal cutoff levels for detecting anxiety based on receiver operating curve analysis.

Scale	Clinical correspondence	Cutoff	Sensitivity	Specificity	AUC	p-value
Total score of PAS	Any anxiety disorders	12.5	88.6%	79.9%	0.847	p<0.001
Persistent anxiety subscale	Generalized anxiety disorder	9.5	89.3%	81.2%	0.875	p<0.001
Episodic anxiety subscale	Panic disorder	4.5	92.1%	81.5%	0.921	p<0.001
Avoidant anxiety subscale	Avoidant anxiety disorders	3.5	78.4%	82.4%	0.835	p<0.001

Anxiety disorders characterized by avoidance are agoraphobia and social phobia (here taken together as avoidant anxiety disorders). ROC = receiver operating characteristics; AUC = area under the curve; PAS = Parkinson Anxiety Scale.

6.3.2. Prevalence of anxiety among Hungarian PD patients

Based on the general threshold (12.5 points), anxiety occurred in 211 patients (35.8%). While persistent anxiety was found in 172 (29.2%), only 122 patients (20.7%) had episodic anxiety and another 99 patients (16.8%) had an avoidant anxiety disorder. Patients with anxiety had more severe PD-related symptoms (higher scores on all domains of MDS-UPDRS), depressive symptoms (BDI and MADRS), worse neurocognitive performance (MDRS and MoCA), and worse HRQoL (measured by PDQ-39).

6.4. Discussion

The aim of the present study was to validate the Hungarian patient-reported version of the PAS by assessing its fundamental clinimetric properties and subsequently determining the prevalence and severity of anxiety among Hungarian PD patients. After a standardized translation and backtranslation of the scale, we initiated a hospital-based validation study on a large diversity of patients having disease severity from minimal to severe. Our results demonstrated excellent data quality, high reliability and validity, and good precision. These findings are consistent with the results of the original [114] and the Italian [115] validation studies.

Based on the obtained cutoff threshold, we identified the prevalence of anxiety among Hungarian PD patients of which 35.8% is in the range of the internationally published rangeA létrejött határérték alapján a magyar PK betegek körében a szorongás gyakorisága 35.8% [109, 110]. Similar to previous findings, we also demonstrated that the presence of anxiety was associated with worse motor performance, cognitive performance, and more severely impaired health-related quality of life[139, 140].

6.5. Conclusions

The Hungarian patient-rated version of the Parkinson Anxiety Scale is a valid, highly reliable, and sensitive tool for assessing the presence and severity of the anxiety symptoms. Although our uniform threshold value may efficiently identify patients with anxiety, different threshold values may be utilized for different disease stages.

7. EXAMINATION OF RELATIONSHIP BETWEEN IMPULSE CONTROL DISORDERS AND INTERNET ADDICTION IN PARKINSON'S DISEASE

7.1. INTRODUCTION

Although the impulse control disorders (ICDs) and related behaviors are increasingly recognized as the side effects of antiparkinsonian medications [141], recent studies demonstrated that compulsive gambling, buying, sexual and eating behaviors, and hobbyism may present in drug naïve Parkinson's disease (PD) [142] as well. Because PD patients with ICDs (PD-ICD) usually feel being ashamed of their compulsive behavior, the majority of them try to hide and deny their overwhelming and uncontrollable problems. Therefore, the correct and early detection of ICD symptoms is quite challenging.

Analyzing the history and behavior of our PD-ICD patients, we recognized that the majority of them performed their compulsive gambling and sexual behavior on the Internet. Moreover, some patients with compulsive buying preferred online shopping over the traditional shopping methods.

We propose that the overuse of Internet or Internet addiction per se might be an indicator for the presence of ICDs, and consequently, the additional screening for the problematic Internet use might help identify PD-ICD patients at earlier stages and higher sensitivity. Taking into consideration the presumable link between Internet overuse and ICDs in PD, we designed a prospective study to test the hypothesis that a screening for excessive Internet use or Internet addiction might improve the identification of PD-ICD patients.

7.2. MATERIALS AND METHODS

In this study, 150 consecutive PD patients fulfilling the UK Brain Bank criteria without known ICD were enrolled. Each patient underwent the screening for ICD in the following sequence:

- The comprehensive neuropsychological examination (including the validated Hungarian versions of the Montreal Cognitive Assessment, MoCA [127, 128], Montgomery-Asberg Depression Rating Scale, MADRS [126], Parkinson Anxiety Scale, PAS [145], and Lille Apathy Rating Scale, LARS[146] for measuring cognition, depression, anxiety and apathy was assessed
- Patients were asked to rate the QUIP.
- Knowing the findings of the neuropsychological assessments and the QUIP, highly

experienced healthcare professional assessed the mMIDI.

- Based on the DSM-V diagnostic criteria for gambling disorder [117] and binge eating [117], and the proposed criteria for compulsive sexual behavior and compulsive buying [147] the patients were categorized as either having or not having ICD problems. This categorization is referred to as the **standard approach** in the manuscript.
- The International Parkinson's Disease and Movement Disorders Society sponsored version of Unified Parkinson's Disease Rating Scale, MDS-UPDRS [118] and the Unified Dyskinesia Rating Scale, UDysRS [148] if applicable, were assessed. The purpose of these tests was not only the phenomenological description of patients but also taking their mind off the topic of ICDs.
- Subsequently, the patients were asked to rate their Internet use by the self-rated Problematic Internet Use Questionnaire (PIUQ) [149].
- Subsequently, the same health care professional reassessed the mMIDI knowing the results of the QUIP and PIUQ. If excessive Internet use was detected, specific questions on the Internet-related habits were also asked. Internet addiction was diagnosed based on the proposed criteria [150]; whereas Internet overuse was defined as the excessive use of the Internet not fulfilling the criteria for Internet addiction. Again, the patients were categorized as either ICD positive or negative **(standard+PIUQ approach**).

To compare the two ICD screening methods (standard vs. standard+PIUQ approaches), nonparametric tests were used (IBM SPSS, version 24.002, Armonk, NY).

7.3. RESULTS

Out of 150 PD patients screened, only 106 patients (70.7%) reported regular Internet use.

Based on the standard evaluation approach, we identified three patients with pathological gambling. However, we found six additional patients with online gambling problems using the standard+PIUQ approach. Therefore, the standard+PIUQ approach performed statistically significantly better (p = 0 031, the McNemar test). The gambler PD-ICD patients identified by only the standard+ PIUQ method had shorter ICD disease duration (6 2 ± 3 4 months vs. 18 4 ± 7 6 months, p < 0 05), milder symptoms and seemingly less serious consequences than the patients picked by the standard approach.

Compulsive sexual problems were recorded in two cases with the standard approach. Based on Internet overuse, another six patients were diagnosed with hypersexuality-type ICDs. Again the standard+PIUQ screening approach was superior (8 vs. 2 patients, p = 0 031, the McNemar test). Patients picked by the PIUQ had apparently milder problems and consequences associated with the ICDs.

As far as the compulsive eating was concerned, both screening methods identified

the same number of patients.

The standard approach demonstrated compulsive buying in seven subjects, whereas the standard+PIUQ method picked eight patients (p = 1 000, the McNemar test).

Hobbyism, punding, and other compulsive problems were identified in seven instances by QUIP and mMIDI alone. Of note, none of the patients reported Internet addiction per se. Using the standard+PIUQ method, a total of 13 patients were picked. Out of these patients, 5 had Internet addiction syndrome per se. Therefore, the standard+PIUQ screening process is superior in identifying hobbyism spectrum ICDs (p = 0 031, the McNemar test).

While the standard approach identified 19 patients out of 106 (17.9%) with any type of ICD, the standard+PIUQ screening process picked 29 patients (27.4%, Supplementary Materials). Therefore, the standard+PIUQ method had a significantly better efficacy (p = 0 004, the McNemar test).

In PD-ICD patients, not only the overall PIUQ score was higher (32 2 ± 5 4 vs. 19 2 ± 0 4, p < 0.001) but also the nonmotor experiences of daily living MDS-UPDRS and the dopamine agonist Levodopa equivalent dosage.

7.4. Discussion

Our pilot study suggests that the screening for problematic Internet use by PIUQ is an effective, feasible, and easy-to-use add-on method for identifying PD-ICD patients more efficiently and probably at earlier stages. Based on our results, compulsive gambling (especially online gambling and betting), hypersexuality, hobbyism/punding, and Internet addiction per se can be more efficiently identified.

7.5. Conclusions

Our pilot study supports the idea that the active screening for Internet overuse or addiction in a PD population may help identify ICD problems with higher accuracy and presumably at earlier stages than the standard approach. Further, preferably longitudinal and multicenter, studies are required to more precisely determine the accuracy of this screening approach.

8. SUMMARY OF NEW RESULTS

The results of my clinical research are as follows:

- For the first time in Hungary, we evaluated the incidence and severity of non-motor symptoms of Parkinson's disease in a large patient population (N = 621). Our findings contribute to the clinical question of whether female sex, as an independent factor, leads to poorer quality of life in Parkinson's disease.
- We performed the validation of the Parkinson's Anxiety Scale on a Hungarian sample to provide a valid, highly reliable, and sensitive tool for measuring the presence and severity of anxiety symptoms in Parkinson's disease.
- For the first time in Hungary, we evaluated the frequency and severity of anxiety in a large sample of patients with Parkinson's disease.
- We have demonstrated that screening for excessive Internet use can more effectively identify the presence of impulse control disorders. We hypothesized that surveying the use of the Internet would not only identify ICD problems with greater accuracy, but also at earlier stages.

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10. LIST OF PUBLICATIONS

10.1. LIST OF PUBLICATIONS BASED ON THE THESIS

Kovács M, Makkos A, Aschermann Zs, Janszky J, Komoly S, Weintraut R, Karadi K, Kovacs N. Impact of sex on the non-motor symptoms and the health-related quality of life in Parkinson's disease. PARKINSONS DISEASE 2016; Paper 7951840. 12 p. **IF: 1.702** Besorolás: Q2

Kovács M, Makkos A, Weintraut R, Janszky J, Kovacs N. Prevalence of anxiety among Hungarian subjects with Parkinson's disease. BEHAVIOURAL NEUROLOGY 2017; Paper 1470149. 7p. **IF: 2.088** Besorolás: Q2

Kovacs M, Makkos A, Pintér D, Juhász A, Darnai G, Karádi K, Janszky J, Norbert K. Screening for problematic Internet use may help identify impulse control disorders in Parkinson's disease. BEHAVIOURAL NEUROLOGY 2019 Paper: 4925015 , 8 p. (2019) **IF: 1.908** Besorolás: Q2

10.2. LIST OF OTHER PUBLICATIONS

1. Kovács, Norbert ; Pál, Endre ; Makkos, Attila ; Kovács, Márton ; Pintér, Dávid. Repetitive transcranial magnetic stimulation can improve anxiety in Parkinson's disease:a randomized, double-blind and controlled trial. BRAIN STIMULATION 12 : 2 pp. 409-409. , 1 p. (2019)
2. Makkos, Attila ; Kovács, Márton ; Pintér, Dávid ; Janszky, József ; Kovács, Norbert. Minimal clinically important difference for the historic parts of the Unified Dyskinesia Rating Scale. PARKINSONISM AND RELATED DISORDERS 58 pp. 79-82. , 4 p. (2019)
3. Makkos-Weisz, Attila ; Kovács, Norbert ; Pál, Endre ; Kovács, Márton ; Pintér, Dávid. Repetitive transcranial magnetic stimulation can improve anxiety in Parkinson's disease: a randomized, double-blind and controlled trial. MOVEMENT DISORDERS 34 : Suppl S2 p. S393 (2019)
4. Pintér, Dávid ; Makkos, Attila ; Kovács, Márton ; Janszky, József ; Kovács, Norbert.Minimal Clinically Important Difference for the Quality of Life in Essential Tremor Questionnaire. MOVEMENT DISORDERS 34 : 5 pp. 759-760. , 2 p. (2019)
5. Pintér, Dávid ; Kovács, Márton ; Harmat, Márk ; Juhász, Annamária ; Janszky, József ; Kovács, Norbert. Trimetazidine and parkinsonism: a prospective study. PARKINSONISM AND RELATED DISORDERS 62 pp. 117-121. , 5 p. (2019)
6. Lucza, Tivadar ; Ascherman, Zsuzsanna ; Kovacs, Marton ; Makkos, Attila ; Harmat, Mark ; Juhasz, Annamaria ; Janszky, Jozsef ; Komoly, Samuel ; Kovacs, Norbert ; Dorn, Krisztina et al. Comparing Sensitivity and Specificity of Addenbrooke's Cognitive Examination-I, III and Mini-Addenbrooke's Cognitive Examination in Parkinson's Disease. BEHAVIOURAL NEUROLOGY 2018 Paper: 5932028 , 9 p. (2018)
7. Makkos, A ; Kovacs, M ; Aschermann, Z ; Harmat, M ; Janszky, J ; Karadi, K ; Kovacs, N. Are the MDS-UPDRS-based composite scores clinically applicable? MOVEMENT DISORDERS 33 : 5 pp. 835-839. , 5 p. (2018)
8. Darnai, G ; Szolcsányi, T ; Hegedüs, G ; Kincses, P ; Kállai, J ; Kovács, M ; Simon, E ; Nagy, Zs ; Janszky, J. Hearing Visuo-tactile Synchrony - Sound-Induced Proprioceptive Drift in the Invisible Hand Illusion. BRITISH JOURNAL OF PSYCHOLOGY 108 : (1) pp. 91-106. , 16 p. (2017)
9. Horváth, Krisztina ; Aschermann, Zsuzsanna ; Kovács, Márton ; Makkos, Attila ; Harmat, Márk ; Janszky, József ; Komoly, Sámuel ; Karádi, Kázmér ; Kovács, Norbert. Minimal clinically important differences for the experiences of daily living parts of MDS-UPDRS. MOVEMENT DISORDERS 32 : 5 pp. 789-793. , 5 p. (2017)
10. Horváth, Krisztina ; Aschermann, Zsuzsanna ; Kovács, Márton ; Makkos, Attila ; Harmat, Márk ; Janszky, József ; Komoly, Sámuel ; Karádi, Kázmér ; Kovács, Norbert. Changes in quality of life in Parkinson's disease: How large must they be to be relevant? NEUROEPIDEMIOLOGY 48 : 1-2 pp. 1-8. , 8 p. (2017)
11. Juhasz, A ; Aschermann, Z ; Acs, P ; Janszky, J ; Kovacs, M ; Makkos, A ; Harmat, M ; Tenyi, D ; Karadi, K ; Komoly, S et al. Levodopa/carbidopa intestinal gel can improve both motor and non-motor experiences of daily living in Parkinson's disease: An open-label study. EUROPEAN JOURNAL OF NEUROLOGY 24 : Suppl. 1 pp. 300-301. , 2 p. (2017)
12. Juhász, A ; Deli, G ; Aschermann, Z ; Janszky, J ; Harmat, M ; Makkos, A ; Kovács, M ; Komoly, S ; Balás, I ; Dóczi, T et al. How Efficient Is Subthalamic Deep Brain Stimulation in Reducing Dyskinesia in Parkinson's Disease? EUROPEAN NEUROLOGY 77 : 5-6 pp. 281-287. , 7 p. (2017)
13. Juhász, Annamária ; Aschermann, Zsuzsanna ; Ács, Péter ; Janszky, József ; Kovács, Márton ; Makkos, Attila ; Harmat, Márk ; Tényi, Dalma ; Karádi, Kázmér ; Komoly, Sámuel et al. Levodopa/carbidopa intestinal gel can improve both motor and non-motor experiences of daily living in Parkinson's disease: an open-label study. PARKINSONISM AND RELATED DISORDERS 37 : 4 pp. 79-86. , 8 p. (2017)

14. Kovács, Márton ; Makkos, Attila ; Janszky, József ; Kovács, Norbert. Independent validation of the quality of life in essential tremor questionnaire (QUEST). IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 70 : 5-6 pp. 193-202. , 10 p. (2017)
15. Kovacs, N ; Juhasz, A ; Zsuzsanna, A ; Janszky, J ; Kovacs, M ; Harmat, M ; Karadi, K ; Makkos, A ; Takats, A ; Toth, A et al. Levodopa/carbidopa intestinal gel can improve both motor and non-motor experiences of daily living in advanced Parkinson's disease. JOURNAL OF THE NEUROLOGICAL SCIENCES 381 : S pp. 123-124. , 2 p. (2017)
16. Kovacs, N ; Juhasz, A ; Aschermann, Z ; Acs, P ; Janszky, J ; Kovacs, M ; Makkos, A ; Harmat, M ; Tenyi, D ; Katadi, K et al. Levodopa/Carbidopa intestinal gel can improve both motor and non-motor experiences of daily living in Parkinson's disease: an open-label study. MOVEMENT DISORDERS 32 : Suppl. 2 Paper: 1430 , 1 p. (2017)
17. A, Makkos ; M, Kovács ; J, Janszky ; N, Kovacs. Independent validation of the quality of life in essential tremor questionnaire (QUEST). EUROPEAN JOURNAL OF NEUROLOGY 23 : Suppl 1 p. 834 (2016)
18. Kovacs, M ; Deli, G ; Aschermann, Z ; Acs, P ; Bosnyak, E ; Janszky, J ; Makkos, A ; Komoly, S ; Kovacs, N. More frequent presence of non-motor symptoms among Hungarian Parkinson's disease patients. EUROPEAN JOURNAL OF NEUROLOGY 23 : Suppl. 2 pp. 650-650. , 1 p. (2016)
19. Kovács, N ; Makkos, A ; Kovács, M ; Janszky, J. Independent validation of the quality of life in essential tremor questionnaire (QUEST). MOVEMENT DISORDERS 31 : Suppl. 2 pp. S517-S517. (2016)
20. Kovács, Norbert ; Deli, Gebriella ; Aschermann, Zsuzsanna ; Makkos, Attila ; Kovács, Márton ; Janszky, József ; Pál, Endre. High frequency repetitive transcranial magnetic stimulation can improve the quality of life and depression in Parkinson's disease: A randomized, double-blind, placebo-controlled study. PARKINSONISM AND RELATED DISORDERS 22 : Suppl. 2. pp. e23-e24. (2016)
21. Kovács, Norbert ; Deli, Gebriella ; Aschermann, Zsuzsanna ; Makkos, Attila ; Janszky, József ; Kovács, Márton. Impact of gender on impulse control disorders and other non-motor symptoms among Parkinson's disease patients. PARKINSONISM AND RELATED DISORDERS 22 : Suppl. 2. pp. e8-e8. (2016)
22. M, Kovács ; G, Deli ; Z, Aschermann ; P, Ács ; E, Bosnyák ; J, Janszky ; A, Makkos ; S, Komoly ; N, Kovacs. More frequent presence of non-motor symptoms among Hungarian Parkinson's disease patients. EUROPEAN JOURNAL OF NEUROLOGY 23 : Suppl 1 p. 681 (2016)
23. N, Kovacs ; G, Deli ; M, Kovács ; A, Makkos ; I, Balás. EP 42. Bilateral subthalamic deep brain stimulation can help preserve working capabilities in Parkinson's disease. CLINICAL NEUROPHYSIOLOGY 127 : 9 p. e193 (2016)
24. N, Kovacs ; R, Weintraut ; A, Makkos ; M, Kovács ; J, Janszky ; K, Karádi. Lille apathy rating scale and MDS-UPDRS for screening apathy in Parkinson's disease.EUROPEAN JOURNAL OF NEUROLOGY 23 : Suppl 1 pp. 504-504. , 1 p. (2016)
25. Weintraut, R ; Karádi, K ; Lucza, T ; Kovács, M ; Makkos, A ; Janszky, J ; Kovács, N. Lille Apathy Rating Scale and MDS-UPDRS for screening apathy in Parkinson's disease. JOURNAL OF PARKINSONS DISEASE 6 : 1 pp. 257-265. , 9 p. (2016)
26. Deli, Gabriella ; Balás, István ; Dóczi, Tamás ; Janszky, József ; Karádi, Kázmér ; Aschermann, Zsuzsanna ; Nagy, Ferenc ; Makkos, Attila ; Kovács, Márton ; Bosnyák, Edit et al. Deep Brain Stimulation Can Preserve Working Status In Parkinson's Disease. PARKINSONS DISEASE 2015 Paper: 936865 , 8 p. (2015)
27. Deli, Gabriella ; Aschermann, Zsuzsanna ; Ács, Péter ; Bosnyák, Edit ; Janszky, József ; Faludi, Béla ; Makkos, Attila ; Kovács, Márton ; Komoly, Sámuel ; Balás, István et al. Bilateral subthalamic stimulation can improve sleep quality in Parkinson's disease. JOURNAL OF PARKINSONS DISEASE 5 : 2 pp. 361-368. , 8 p. (2015)
28. Horváth, Krisztina ; Aschermann, Zsuzsanna ; Ács, Péter ; Deli, Gabriella ; Janszky, József ; Komoly, Sámuel ; Karádi, Kázmér ; Kovács, Márton ; Makkos, Attila ; Faludi, Béla et al. Minimal clinically important difference on Parkinson's Disease Sleep Scale 2nd version (PDSS-2). PARKINSONS DISEASE 2015 Paper: 970534 , 8 p. (2015)
29. Lucza, Tivadar ; Karádi, Kázmér ; Komoly, Sámuel ; Janszky, József ; Kállai, János ; Makkos, Attila ; Kovács, Márton ; Weintraut, Rita ; Deli, Gabriella ; Aschermann, Zsuzsanna et al. Neurokognitív zavarok diagnosztizálási és kezelési lehetőségei Parkinson-kórban. ORVOSI HETILAP 156 : 23 pp. 915-926. , 12 p. (2015)

11. REFERENCES

[1] *Bereczki D* (**2010**) The description of all four cardinal signs of Parkinson's disease in a Hungarian medical text published in 1690. *Parkinsonism Relat Disord* 16, 290-293.

[2] *Parkinson J* (**2002**) An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci* 14, 223-236; discussion 222.

[3] *Hidasi E* (**2010**) A Parkinson-kór modern szemlélete. *Lege artis medicinae* 20, 825-829.

[7] *Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G* (**2015**) MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 30, 1591-1601.

[9] *Berg D, Postuma RB, Bloem B, Chan P, Dubois B, Gasser T, Goetz CG, Halliday GM, Hardy J, Lang AE, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G* (**2014**) Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. *Mov Disord* 29, 454-462.

[14] *Litvan I, Bhatia KP, Burn DJ, Goetz CG, Lang AE, McKeith I, Quinn N, Sethi KD, Shults C, Wenning GK* (**2003**) Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord* 18, 467-486.

[15] *Gelb DJ, Oliver E, Gilman S* (**1999**) Diagnostic criteria for Parkinson disease. *Arch Neurol* 56, 33-39.

[16] *Daniel SE, Lees AJ* (**1993**) Parkinson's Disease Society Brain Bank, London: overview and research. *J Neural Transm Suppl* 39, 165-172.

[17] *Goetz CG, Nutt JG, Stebbins GT* (**2008**) The Unified Dyskinesia Rating Scale: presentation and clinimetric profile. *Mov Disord* 23, 2398-2403.

[18] *Chaudhuri KR, Schapira AH* (**2009**) Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* 8, 464-474.

[20] *Santos-Garcia D, de la Fuente-Fernandez R* (**2013**) Impact of non-motor symptoms on health-related and perceived quality of life in Parkinson's disease. *J Neurol Sci* 332, 136-140.

[21] *Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR* (**2011**) The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord* 26, 399-406.

[22] *Kadastik-Eerme L, Rosenthal M, Paju T, Muldmaa M, Taba P* (**2015**) Health-related quality of life in Parkinson's disease: a cross-sectional study focusing on non-motor symptoms. *Health Qual Life Outcomes* 13, 83.

[23] *Martinez-Martin P, Falup Pecurariu C, Odin P, van Hilten JJ, Antonini A, Rojo-Abuin JM, Borges V, Trenkwalder C, Aarsland D, Brooks DJ, Ray Chaudhuri K* (**2012**) Gender-related differences in the burden of non-motor symptoms in Parkinson's disease. *J Neurol* 259, 1639-1647.

[25] *van der Hoek TC, Bus BA, Matui P, van der Marck MA, Esselink RA, Tendolkar I* (**2011**) Prevalence of depression in Parkinson's disease: effects of disease stage, motor subtype and gender. *J Neurol Sci* 310, 220-224.

[34] *Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE* (**2011**) Symptomatology and markers of anxiety disorders in Parkinson's disease: a cross-sectional study. *Mov Disord* 26, 484-492.

[35] *Guo X, Song W, Chen K, Chen X, Zheng Z, Cao B, Huang R, Zhao B, Wu Y, Shang HF* (**2013**) Gender and onset age-related features of non-motor symptoms of patients with Parkinson's disease--a study from Southwest China. *Parkinsonism Relat Disord* 19, 961-965.

[36] *Beiske AG, Loge JH, Ronningen A, Svensson E* (**2009**) Pain in Parkinson's disease: Prevalence and characteristics. *Pain* 141, 173-177.

[38] *Bronner G, Cohen OS, Yahalom G, Kozlova E, Orlev Y, Molshatzki N, Strauss H, Hassin-Baer S* (**2014**) Correlates of quality of sexual life in male and female patients with Parkinson disease and their partners. *Parkinsonism Relat Disord* 20, 1085-1088.

[39] *Szewczyk-Krolikowski K, Tomlinson P, Nithi K, Wade-Martins R, Talbot K, Ben-Shlomo Y, Hu MT* (**2014**) The influence of age and gender on motor and non-motor features of early Parkinson's disease: initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort. *Parkinsonism Relat Disord* 20, 99-105.

[40] *Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, Stern MB, Tilley BC, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, Van Hilten JJ, LaPelle N* (**2007**) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. *Mov Disord* 22, 41-47.

[41] *Horváth K, Aschermann Z, Ács P, Bosnyák E, Deli G, Pál E, Késmárki I, Horváth R, Takács K, Komoly S, Bokor M, Rigó E, Lajtos J, Klivenyi P, Dibo G, Vécsei L, Takáts A, Tóth A, Imre P, Nagy F, Herceg M, Hidasi E, Kovács N* (**2014**) Az MDS-UPDRS magyar validációja: Miért szükséges újabb Parkinson-pontozóskála? *Ideggyogy Sz* 67, 129–134.

[42] *Hoehn MM, Yahr MD* (**1967**) Parkinsonism: onset, progression and mortality. *Neurology* 17, 427-442.

[47] *Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, Pezzela FR, Forbes A, Hogl B, Trenkwalder C* (**2002**) The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 73, 629-635.

[48] *Trenkwalder C, Kohnen R, Hogl B, Metta V, Sixel-Doring F, Frauscher B, Hulsmann J, Martinez-Martin P, Chaudhuri KR* (**2011**) Parkinson's disease sleep scale--validation of the revised version PDSS-2. *Mov Disord* 26, 644-652.

[49] *Horvath K, Aschermann Z, Acs P, Deli G, Janszky J, Karadi K, Komoly S, Faludi B, Kovacs N* (**2014**) Test-Retest Validity of Parkinson's Disease Sleep Scale 2nd Version (PDSS-2). *J Parkinsons Dis* 4, 687-691.

[50] *Kovács N, Horváth K, Aschermann Z, Ács P, Bosnyák E, Deli G, Pál E, Janszky J, Faludi B, Karádi K, Késmárki I, Bokor M, Rigó E, Lajtos J, Klivényi P, Dibó G, Vécsei L, Takáts A, Tóth A, Imre P, Nagy F, Herceg M, Kamondi A, Hidasi E, Komoly S* (**2016**) Independent validation of Parkinson's disease Sleep Scale 2nd version (PDSS-2). *Sleep Biol Rhythms* 14, 63-73.

[51] *Kovács N, Pál E, Janszky J, Bosnyák E, Ács P, Aschermann Z, Faludi B* (**2013**) Parkinson's disease Sleep Scale-2 and Epworth Sleep Scale. *J Neurol Sci* 333, e139.

[52] *Pál E, Nagy F, Aschermann Z, Balázs É, Kovács N* (**2010**) The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: a randomized, double-blind, placebo-controlled study. *MOVEMENT DISORDERS* 25, 2311-2317.

[53] *Leentjens AF, Dujardin K, Marsh L, Richard IH, Starkstein SE, Martinez-Martin P* (**2011**) Anxiety rating scales in Parkinson's disease: a validation study of the Hamilton anxiety rating scale, the Beck anxiety inventory, and the hospital anxiety and depression scale. *Mov Disord* 26, 407-415.

[54] *Sockeel P, Dujardin K, Devos D, Deneve C, Destee A, Defebvre L* (**2006**) The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 77, 579-584.

[55] *Kaszás B, Kovács N, Balás I, Kállai J, Aschermann Z, Kerekes Z, Komoly S, Nagy F, Janszky J, Lucza T, Karádi K* (**2012**) Sensitivity and specificity of Addenbrooke's Cognitive Examination, Mattis Dementia Rating Scale, Frontal Assessment Battery and Mini Mental State Examination for diagnosing dementia in Parkinson's disease. *Parkinsonism Relat Disord* 18, 553-556.

[56] *Lucza T, Karadi K, Kallai J, Weintraut R, Janszky J, Makkos A, Komoly S, Kovacs N* (**2015**) Screening Mild and Major Neurocognitive Disorders in Parkinson's Disease. *Behav Neurol* 2015, 983606.

[58] *Weintraub D, Hoops S, Shea JA, Lyons KE, Pahwa R, Driver-Dunckley ED, Adler CH, Potenza MN, Miyasaki J, Siderowf AD, Duda JE, Hurtig HI, Colcher A, Horn SS, Stern MB, Voon V* (**2009**) Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Mov Disord* 24, 1461-1467.

[59] *Fazekas G, Kulmann L* (**2001**) Parkinsonos betegek életminőségét vizsgáló kérdőív (PDQ-39) magyarországi adaptációja [Hungarian adaption of the PDQ-39 in Parkinson's disease]. *Ideggyogy Sz* 54, 42-44.

[60] *Szende A, Nemeth R* (**2003**) A magyar lakosság egészségi állapothoz kapcsolódó életminősége. *Orv Hetil* 144, 1667-1674.

[63] *Scott B, Borgman A, Engler H, Johnels B, Aquilonius SM* (**2000**) Gender differences in Parkinson's disease symptom profile. *Acta Neurol Scand* 102, 37-43.

[64] *Roland KP, Jakobi JM, Powell C, Jones GR* (**2011**) Factors related to functional independence in females with Parkinson's disease: a systematic review. *Maturitas* 69, 304-311.

[65] *Lyons KE, Hubble JP, Troster AI, Pahwa R, Koller WC* (**1998**) Gender differences in Parkinson's disease. *Clin Neuropharmacol* 21, 118-121.

[66] *Rascol O, Perez-Lloret S, Damier P, Delval A, Derkinderen P, Destee A, Meissner WG, Tison F, Negre-Pages L* (**2015**) Falls in ambulatory non-demented patients with Parkinson's disease. *J Neural Transm (Vienna)* 122, 1447-1455.

[67] *Grimbergen YA, Schrag A, Mazibrada G, Borm GF, Bloem BR* (**2013**) Impact of falls and fear of falling on health-related quality of life in patients with Parkinson's disease. *J Parkinsons Dis* 3, 409-413.

[68] *Michalowska M, Fiszer U, Krygowska-Wajs A, Owczarek K* (**2005**) Falls in Parkinson's disease. Causes and impact on patients' quality of life. *Funct Neurol* 20, 163-168.

[69] *Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N* (**2008**) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 23, 2129-2170.

[70] *Hanagasi HA, Akat S, Gurvit H, Yazici J, Emre M* (**2011**) Pain is common in Parkinson's disease. *Clin Neurol Neurosurg* 113, 11-13.

[71] *Khedr EM, El Fetoh NA, Khalifa H, Ahmed MA, El Beh KM* (**2013**) Prevalence of non motor features in a cohort of Parkinson's disease patients. *Clin Neurol Neurosurg* 115, 673-677.

[72] *Picillo M, Amboni M, Erro R, Longo K, Vitale C, Moccia M, Pierro A, Santangelo G, De Rosa A, De Michele G, Santoro L, Orefice G, Barone P, Pellecchia MT* (**2013**) Gender differences in non-motor symptoms in early, drug naive Parkinson's disease. *J Neurol* 260, 2849-2855.

[73] *Picillo M, Erro R, Amboni M, Longo K, Vitale C, Moccia M, Pierro A, Scannapieco S, Santangelo G, Spina E, Orefice G, Barone P, Pellecchia MT* (**2014**) Gender differences in non-motor symptoms in early Parkinson's disease: a 2-years follow-up study on previously untreated patients. *Parkinsonism Relat Disord* 20, 850-854.

[74] *Menon B, Nayar R, Kumar S, Cherkil S, Venkatachalam A, Surendran K, Deepak KS* (**2015**) Parkinson's Disease, Depression, and Quality-of-Life. *Indian J Psychol Med* 37, 144-148.

[75] *Wee N, Kandiah N, Acharyya S, Chander RJ, Ng A, Au WL, Tan LC* (**2015**) Depression and anxiety are co-morbid but dissociable in mild Parkinson's disease: A prospective longitudinal study of patterns and predictors. *Parkinsonism Relat Disord*.

[76] *Stocchi F, Abbruzzese G, Ceravolo R, Cortelli P, D'Amelio M, De Pandis MF, Fabbrini G, Pacchetti C, Pezzoli G, Tessitore A, Canesi M, Iannacone C, Zappia M, Group FS* (**2014**) Prevalence of fatigue in Parkinson disease and its clinical correlates. *Neurology* 83, 215-220.

[77] *Hagell P, Brundin L* (**2009**) Towards an understanding of fatigue in Parkinson disease. *J Neurol Neurosurg Psychiatry* 80, 489-492.
[78] *Phu AL, Xu Z, Brakoulias V, Mahant N, Fung VS, Moore GD, Martin A, Starcevic V, Krause M* (**2014**) Effect of impulse control disorders on disability and quality of life in Parkinson's disease patients. *J Clin Neurosci* 21, 63-66.
[79] *Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Duda JE, Moberg PJ, Stern MB* (**2006**) Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Arch Neurol* 63, 969-973.
[80] *Isaias IU, Siri C, Cilia R, De Gaspari D, Pezzoli G, Antonini A* (**2008**) The relationship between impulsivity and impulse control disorders in Parkinson's disease. *Mov Disord* 23, 411-415.
[81] *Mestre TA, Strafella AP, Thomsen T, Voon V, Miyasaki J* (**2013**) Diagnosis and treatment of impulse control disorders in patients with movement disorders. *Ther Adv Neurol Disord* 6, 175-188.
[82] *Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, Whetteckey J, Wunderlich GR, Lang AE* (**2010**) Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* 67, 589-595.
[83] *Lubomski M, Louise Rushworth R, Lee W, Bertram KL, Williams DR* (**2014**) Sex differences in Parkinson's disease. *J Clin Neurosci* 21, 1503-1506.
[84] *Soh SE, McGinley JL, Watts JJ, Iansek R, Murphy AT, Menz HB, Huxham F, Morris ME* (**2013**) Determinants of health-related quality of life in people with Parkinson's disease: a path analysis. *Qual Life Res* 22, 1543-1553.
[85] *Winter Y, von Campenhausen S, Popov G, Reese JP, Balzer-Geldsetzer M, Kukshina A, Zhukova TV, Bertschi N, Botzel K, Gusev E, Oertel WH, Dodel R, Guekht A* (**2010**) Social and clinical determinants of quality of life in Parkinson's disease in a Russian cohort study. *Parkinsonism Relat Disord* 16, 243-248.
[86] *Karlsen KH, Larsen JP, Tandberg E, Maland JG* (**1998**) Quality of life measurements in patients with Parkinson's disease: A community-based study. *Eur J Neurol* 5, 443-450.
[87] *Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F* (**2005**) Impact of the motor complications of Parkinson's disease on the quality of life. *Mov Disord* 20, 224-230.
[88] *Carod-Artal FJ, Vargas AP, Martinez-Martin P* (**2007**) Determinants of quality of life in Brazilian patients with Parkinson's disease. *Mov Disord* 22, 1408-1415.
[89] *Carod-Artal FJ, Ziomkowski S, Mourao Mesquita H, Martinez-Martin P* (**2008**) Anxiety and depression: main determinants of health-related quality of life in Brazilian patients with Parkinson's disease. *Parkinsonism Relat Disord* 14, 102-108.
[90] *Andreadou E, Anagnostouli M, Vasdekis V, Kararizou E, Rentzos M, Kontaxis T, Evdokimidis I* (**2011**) The impact of comorbidity and other clinical and sociodemographic factors on health-related quality of life in Greek patients with Parkinson's disease. *Aging Ment Health* 15, 913-921.
[91] *Morley D, Dummett S, Kelly L, Dawson J, Jenkinson C* (**2015**) Evaluating the psychometric properties of an e-based version of the 39-item Parkinson's Disease Questionnaire. *Health Qual Life Outcomes* 13, 5.
[92] *McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD* (**1994**) The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 32, 40-66.
[93] *Morimoto T, Shimbo T, Orav JE, Matsui K, Goto M, Takemura M, Hira K, Fukui T* (**2003**) Impact of social functioning and vitality on preference for life in patients with Parkinson's disease. *Mov Disord* 18, 171-175.
[94] *Qin Z, Zhang L, Sun F, Fang X, Meng C, Tanner C, Chan P* (**2009**) Health related quality of life in early Parkinson's disease: impact of motor and non-motor symptoms, results from Chinese levodopa exposed cohort. *Parkinsonism Relat Disord* 15, 767-771.
[95] *Klepac N, Pikija S, Kraljic T, Relja M, Trkulja V, Juren S, Pavlicek I, Babic T* (**2007**) Association of rural life setting and poorer quality of life in Parkinson's disease patients: a cross-sectional study in Croatia. *Eur J Neurol* 14, 194-198.
[96] *Marras C, Lang A, Krahn M, Tomlinson G, Naglie G, Parkinson Study G* (**2004**) Quality of life in early Parkinson's disease: impact of dyskinesias and motor fluctuations. *Mov Disord* 19, 22-28.
[97] *Martinez-Martin P, Serrano-Duenas M, Forjaz MJ, Serrano MS* (**2007**) Two questionnaires for Parkinson's disease: are the PDQ-39 and PDQL equivalent? *Qual Life Res* 16, 1221-1230.
[98] *Behari M, Srivastava AK, Pandey RM* (**2005**) Quality of life in patients with Parkinson's disease. *Parkinsonism Relat Disord* 11, 221-226.
[99] *Fereshtehnejad SM, Shafieesabet M, Farhadi F, Hadizadeh H, Rahmani A, Naderi N, Khaefpanah D, Shahidi GA, Delbari A, Lokk J* (**2015**) Heterogeneous Determinants of Quality of Life in Different Phenotypes of Parkinson's Disease. *PLoS ONE* 10, e0137081.
[100] *Hristova DR, Hristov JI, Mateva NG, Papathanasiou JV* (**2009**) Quality of life in patients with Parkinson's disease. *Folia Med (Plovdiv)* 51, 58-64.
[101] *Winter Y, von Campenhausen S, Gasser J, Seppi K, Reese JP, Pfeiffer KP, Botzel K, Oertel WH, Dodel R, Poewe W* (**2010**) Social and clinical determinants of quality of life in Parkinson's disease in Austria: a cohort study. *J Neurol* 257, 638-645.
[102] *Zhao YJ, Tan LC, Lau PN, Au WL, Li SC, Luo N* (**2008**) Factors affecting health-related quality of life amongst Asian patients with Parkinson's disease. *Eur J Neurol* 15, 737-742.
[103] *Wu Y, Guo XY, Wei QQ, Song W, Chen K, Cao B, Ou RW, Zhao B, Shang HF* (**2014**) Determinants of the quality of life in Parkinson's disease: results of a cohort study from Southwest China. *J Neurol Sci* 340, 144-149.
[104] *Spadaro L, Bonanno L, Di Lorenzo G, Bramanti P, Marino S* (**2013**) Health-related quality of life in Parkinson's disease patients in northeastern Sicily, Italy: (An ecological perspective). *Neural Regen Res* 8, 1615-1622.

[105] *Mitra S, Chakrabarti N, Dutta SS, Ray S, Bhattacharya P, Sinha P, Bhattacharyya A* (**2015**) Gender-specific brain regional variation of neurons, endogenous estrogen, neuroinflammation and glial cells during rotenone-induced mouse model of Parkinson's disease. *Neuroscience* 292, 46-70.

[106] *Nakaso K, Horikoshi Y, Takahashi T, Hanaki T, Nakasone M, Kitagawa Y, Koike T, Matsura T* (**2016**) Estrogen receptor-mediated effect of delta-tocotrienol prevents neurotoxicity and motor deficit in the MPTP mouse model of Parkinson's disease. *Neurosci Lett* 610, 117-122.

[107] *Adams C, Kumar R* (**2013**) The effect of estrogen in a man with Parkinson's disease and a review of its therapeutic potential. *Int J Neurosci* 123, 741-742.

[108] *Parkinson Study Group PI* (**2011**) A randomized pilot trial of estrogen replacement therapy in post-menopausal women with Parkinson's disease. *Parkinsonism Relat Disord* 17, 757-760.

[109] *Broen MP, Narayen NE, Kuijf ML, Dissanayaka NN, Leentjens AF* (**2016**) Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord* 31, 1125-1133.

[110] *Dissanayaka NN, Sellbach A, Matheson S, O'Sullivan JD, Silburn PA, Byrne GJ, Marsh R, Mellick GD* (**2010**) Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Mov Disord* 25, 838-845.

[114] *Leentjens AF, Dujardin K, Pontone GM, Starkstein SE, Weintraub D, Martinez-Martin P* (**2014**) The Parkinson Anxiety Scale (PAS): development and validation of a new anxiety scale. *Mov Disord* 29, 1035-1043.

[115] *Santangelo G, Falco F, D'Iorio A, Cuoco S, Raimo S, Amboni M, Pellecchia MT, Longo K, Vitale C, Barone P* (**2016**) Anxiety in early Parkinson's disease: Validation of the Italian observer-rated version of the Parkinson Anxiety Scale (OR-PAS). *J Neurol Sci* 367, 158-161.

[117] *American Psychiatric Association* (**2013**) *Diagnostic and statistical manual of mental disorders*, American Psychiatric Publishing, Arlington, VA.

[118] *Horváth K, Aschermann Z, Ács P, Bosnyák E, Deli G, Pál E, Késmárki I, Horváth R, Takács K, Komoly S, Bokor M, Rigó E, Lajtos J, Klivényi P, Dibó G, Vécsei L, Takáts A, Tóth A, Imre P, Nagy F, Herceg M, Hidasi E, Kovács N* (**2014**) Validation of the Hungarian MDS-UPDRS: Why do we need a new Parkinson scale? *Ideggyogy Sz* 67, 129–134.

[119] *Horvath K, Aschermann Z, Acs P, Deli G, Janszky J, Komoly S, Balazs E, Takacs K, Karadi K, Kovacs N* (**2015**) Minimal clinically important difference on the Motor Examination part of MDS-UPDRS. *Parkinsonism Relat Disord* 21, 1421-1426.

[120] *Horvath K, Aschermann Z, Kovacs M, Makkos A, Harmat M, Janszky J, Komoly S, Karadi K, Kovacs N* (**2017**) Minimal clinically important differences for the experiences of daily living parts of movement disorder society-sponsored unified Parkinson's disease rating scale. *Mov Disord* 32, 789-793.

[122] *Martinez-Martin P, Rodriguez-Blazquez C, Abe K, Bhattacharyya KB, Bloem BR, Carod-Artal FJ, Prakash R, Esselink RA, Falup-Pecurariu C, Gallardo M, Mir P, Naidu Y, Nicoletti A, Sethi K, Tsuboi Y, van Hilten JJ, Visser M, Zappia M, Chaudhuri KR* (**2009**) International study on the psychometric attributes of the non-motor symptoms scale in Parkinson disease. *Neurology* 73, 1584-1591.

[123] *Kovacs M, Makkos A, Aschermann Z, Janszky J, Komoly S, Weintraut R, Karadi K, Kovacs N* (**2016**) Impact of Sex on the Nonmotor Symptoms and the Health-Related Quality of Life in Parkinson's Disease. *Parkinsons Dis* 2016, 7951840.

[124] *Deli G, Aschermann Z, Acs P, Bosnyak E, Janszky J, Faludi B, Makkos A, Kovacs M, Komoly S, Balas I, Doczi T, Kovacs N* (**2015**) Bilateral subthalamic stimulation can improve sleep quality in Parkinson's disease. *J Parkinsons Dis* 5, 361-368.

[125] *Weintraut R, Karádi K, Lucza T, Kovács M, Makkos A, Janszky J, Kovács N* (**2016**) Lille Apathy Rating Scale and MDS-UPDRS for screening apathy in Parkinson's disease. *JOURNAL OF PARKINSONS DISEASE* 6, 257-265.

[126] *Kaszas B, Kovacs N, Balas I, Kallai J, Aschermann Z, Kerekes Z, Komoly S, Nagy F, Janszky J, Lucza T, Karadi K* (**2012**) Sensitivity and specificity of Addenbrooke's Cognitive Examination, Mattis Dementia Rating Scale, Frontal Assessment Battery and Mini Mental State Examination for diagnosing dementia in Parkinson's disease. *Parkinsonism Relat Disord* 18, 553-556.

[127] *Lucza T, Karadi K, Kallai J, Weintraut R, Janszky J, Makkos A, Komoly S, Kovacs N* (**2015**) Screening Mild and Major Neurocognitive Disorders in Parkinson's Disease. *Behav Neurol* 2015, 983606.

[128] *Lucza T, Karadi K, Komoly S, Janszky J, Kallai J, Makkos A, Kovacs M, Weintraut R, Deli G, Aschermann Z, Kovacs N* (**2015**) Neurocognitive disorders in Parkinson's disease. *Orv Hetil* 156, 915-926.

[129] *Kovacs N, Aschermann Z, Acs P, Bosnyak E, Deli G, Janszky J, Komoly S* (**2014**) Levodopa/carbidopa intestinalis gél kezelés hatása az életminőségre [The impact of levodopa-carbidopa intestinal gel on health-related quality of life in Parkinson's disease]. *Ideggyogy Sz* 67, 245–250.

[130] *Horvath K, Aschermann Z, Kovacs M, Makkos A, Harmat M, Janszky J, Komoly S, Karadi K, Kovacs N* (**2017**) Changes in Quality of Life in Parkinson's Disease: How Large Must They Be to Be Relevant? *Neuroepidemiology* 48, 1-8.

[131] *Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ* (**2004**) Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome. *Health Technol Assess* 8, iii, 1-48.

[132] *McHorney CA, Tarlov AR* (**1995**) Individual-patient monitoring in clinical practice: are available health status surveys adequate? *Qual Life Res* 4, 293-307.

[133] *Hays RD, Anderson R, Revicki D* (**1993**) Psychometric considerations in evaluating health-related quality of life measures. *Qual Life Res* 2, 441-449.

[135] *Kovács N, Horváth K, Aschermann Z, Ács P, Bosnyák E, Deli G, Pál E, Janszky J, Faludi B, Karádi K, Késmárki I, Bokor M, Rigó E, Lajtos J, Klivényi P, Dibó G, Vécsei L, Takáts A, Tóth A, Imre P, Nagy F, Herceg M, Kamondi A, Hidasi E,*

Komoly S (**2016**) Independent validation of Parkinson's disease Sleep Scale 2nd version (PDSS-2). *Sleep and Biological Rhythms* 14, 63-73.

[136] *Aaronson N, Alonso J, Burnam A, Lohr KN, Patrick DL, Perrin E, Stein RE* (**2002**) Assessing health status and quality-of-life instruments: attributes and review criteria. *Qual Life Res* 11, 193-205.

[138] *Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A* (**2001**) The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain* 124, 962-973.

[139] *Dissanayaka NN, Lawson RA, Yarnall AJ, Duncan GW, Breen DP, Khoo TK, Barker RA, Burn DJ, group I-Ps* (**2017**) Anxiety is associated with cognitive impairment in newly-diagnosed Parkinson's disease. *Parkinsonism Relat Disord* 36, 63-68.

[140] *Broen MP, Kohler S, Moonen AJ, Kuijf ML, Dujardin K, Marsh L, Richard IH, Starkstein SE, Martinez-Martin P, Leentjens AF* (**2016**) Modeling anxiety in Parkinson's disease. *Mov Disord* 31, 310-316.

[141] *Biundo R, Weis L, Abbruzzese G, Calandra-Buonaura G, Cortelli P, Jori MC, Lopiano L, Marconi R, Matinella A, Morgante F, Nicoletti A, Tamburini T, Tinazzi M, Zappia M, Vorovenci RJ, Antonini A* (**2017**) Impulse control disorders in advanced Parkinson's disease with dyskinesia: The ALTHEA study. *Mov Disord* 32, 1557-1565.

[142] *Antonini A, Siri C, Santangelo G, Cilia R, Poletti M, Canesi M, Caporali A, Mancini F, Pezzoli G, Ceravolo R, Bonuccelli U, Barone P* (**2011**) Impulsivity and compulsivity in drug-naive patients with Parkinson's disease. *Mov Disord* 26, 464-468.

[145] *Kovacs M, Makkos A, Weintraut R, Karadi K, Janszky J, Kovacs N* (**2017**) Prevalence of Anxiety among Hungarian Subjects with Parkinson's Disease. *Behav Neurol* 2017, 1470149.

[146] *Weintraut R, Karadi K, Lucza T, Kovacs M, Makkos A, Janszky J, Kovacs N* (**2016**) Lille Apathy Rating Scale and MDS-UPDRS for Screening Apathy in Parkinson's Disease. *J Parkinsons Dis* 6, 257-265.

[147] *Voon V, Fox SH* (**2007**) Medication-related impulse control and repetitive behaviors in Parkinson disease. *Arch Neurol* 64, 1089-1096.

[148] *Horvath K, Aschermann Z, Acs P, Bosnyak E, Deli G, Pal E, Kesmarki I, Horvath R, Takacs K, Balazs E, Komoly S, Bokor M, Rigo E, Lajtos J, Takats A, Toth A, Klivenyi P, Dibo G, Vecsei L, Hidasi E, Nagy F, Herceg M, Imre P, Kovacs N* (**2015**) Az Egységesített Dyskinesia Pontozóskála magyar nyelvi validációja [Validation of the Hungarian Unified Dyskinesia Rating Scale]. *Ideggyogy Sz* 68, 183-188.

[149] *Demetrovics Z, Szeredi B, Rozsa S* (**2008**) The three-factor model of Internet addiction: the development of the Problematic Internet Use Questionnaire. *Behav Res Methods* 40, 563-574.

[150] *Shapira Nathan A, Lessig Mary C, Goldsmith Toby D, Szabo Steven T, Lazoritz M, Gold Mark S, Stein Dan J* (**2003**) Problematic internet use: Proposed classification and diagnostic criteria. *Depression and Anxiety* 17, 207-216.