New developments in the diagnosis and treatment of movement disorders

Doctoral (PhD) thesis

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ABBREVIATIONS

AUC	area under the curve
DBS	deep brain stimulation
EMA	European Medicines Agency
ET	essential tremor
HRQoL	health-related quality of life
HYS	Hoehn-Yahr stage
MCID	minimal clinically important difference
MDS-UPDRS	Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale
PD	Parkinson's disease
PDCS	Parkinson's Disease Composite Scale
PDQ-39	39-item Parkinson's Disease Questionnaire
PGI-I	Patient-rated Global Impression – Improvement
QUEST	Quality of Life in Essential Tremor Questionnaire
ROC	receiver operating characteristic
TMZ	trimetazidine

1. INTRODUCTION

Movement disorders are a diverse group of central nervous system diseases that impair movement execution and coordination and are also characterized by involuntary movements while the primary motor and sensory systems remain relatively intact. My research activity has mainly focused on disorders causing parkinsonism and tremor.

1.1. Parkinsonism

Parkinsonism is a clinical syndrome characterized by bradykinesia (the combination of slowness and progressive reduction of amplitude and/or speed of movements) and rigidity (the simultaneous increase of tones of both agonist and antagonist muscles) with or without resting tremor [1]. The most frequent causes of parkinsonism are Parkinson's disease (PD) and disorders causing non-neurodegenerative, secondary parkinsonism.

1.1.1. Parkinson's disease

PD is the second most common neurodegenerative disorder after Alzheimer's disease [2]. At present, the disease affects approximately 0.1-0.2% of the total world population (approximately 7.5-15 million people) [3], while in Hungary, the estimated number of patients with PD is 20-40 thousand [4].

The neuropathologic basis of PD is the development of Lewy-bodies, protein inclusions containing alpha-synuclein, predominantly in the lateral part of the substantia nigra called pars compacta. The exact etiology of the disease is still unknown, both genetic and environmental factors seem to play a role in the development of PD [2].

In addition to the cardinal motor symptoms of parkinsonism, several other motor (e.g., postural instability, dyskinesia) and nonmotor symptoms (e.g., depression, apathy, and anxiety) can occur in PD [5-9], and they can seriously impair the health-related quality of life (HRQoL) [10].

At present, the diagnosis of PD is based on the careful evaluation of clinical symptoms [5]. Additional procedures (e.g., brain imaging, laboratory tests, ophthalmological examination, genetic tests, and acute levodopa challenge) are mainly useful in the differential diagnosis of parkinsonism [2].

PD is currently incurable. In the symptomatic treatment of the disease, oral medications (e.g., levodopa, dopamine agonists) and device-aided therapies [e.g., deep brain stimulation (DBS), levodopa-carbidopa intestinal gel infusion] are available [11]. In the first few years of PD, oral medications can provide highly effective symptomatic control ("honeymoon" period) in most of the cases. However, in advanced PD, motor and nonmotor fluctuations and side effects of antiparkinsonian drugs can occur, therefore, the combination of oral antiparkinsonian medications and the initiation of device-aided treatments may become necessary. Based on comorbidities, age, and clinical stage of PD, medications for neuropsychiatric (e.g., mood problems, neurocognitive disorders, and psychosis), urogenital, gastrointestinal, and sleep disorders may also need to be added to antiparkinsonian treatments [11].

1.1.2. Drug-induced parkinsonism

After PD, certain drugs cause parkinsonism most commonly, and drug-induced parkinsonism represents the largest portion of cases with secondary parkinsonism [12].

Typical antipsychotics (e.g., haloperidol, chlorpromazine) and antidepressants (e.g., sertraline) are most frequently responsible for drug-induced parkinsonism [13], however, several other medications (e.g., antiemetics, antiepileptics, antianginal medications, and preventive drugs for migraine) have been shown to induce parkinsonism [13]. These drugs can process postsynaptic inhibition of dopamine receptors by passing the blood-brain barrier [14]. Risk factors for developing drug-induced parkinsonism include older age [15], female sex [16], higher doses of the drug, longer duration of the treatment, and the type of agent used [15].

Drug-induced parkinsonism is typically characterized by symmetrical rigidity and bradykinesia [13, 17], however, other motor features (e.g., orofacial dyskinesia) may also appear [17]. In addition to motor symptoms, cognitive impairment and orthostatic hypotension may also be present [18, 19].

Symmetrical motor symptoms, the dominance of rigidity and bradykinesia, presence of oromandibular dyskinesia, absence or low level of levodopa response, use of medications known to induce parkinsonism, and complete disappearance of symptoms after the withdrawal of the drug support the diagnosis of drug-induced parkinsonism [17]. In addition, DaTSCAN may also help diagnose parkinsonism caused by drugs [20]. However, follow-up of patients is often necessary to confirm or refute the diagnosis of drug-induced parkinsonism [16, 21].

In the treatment of drug-induced parkinsonism, discontinuation of the drug that is suspected to be responsible for the symptoms and/or the change of this medication to another one that is less prone to induce parkinsonism (e.g., the change of typical antipsychotics to atypical ones that do not or barely cause parkinsonism) are among the most important steps. These interventions can even lead to the complete disappearance of parkinsonism [22]. However, even after complete remission, PD may later develop in patients with drug-induced parkinsonism in the history [16, 21]. This sheds light on the importance of the follow-up of patients with drug-induced parkinsonism.

1.2. Essential tremor

Tremor is defined as the rhythmical, alternating, and involuntary contractions of striated muscles. The main tremor types are rest and action tremor. Action tremor can be further divided into postural and kinetic tremor. Essential tremor (ET), a chronic and progressive neurological disease, is the most common cause for action tremor. It is also the most common movement disorder, its prevalence is estimated to be 4 to 39 per 1000 [23, 24].

The exact neuropathologic basis and etiology of ET are currently unknown. The etiology of the disease appears to be multifactorial, meaning that both genetic [25] and environmental factors [26] seem to play a role in the development of ET.

ET was considered as a benign and monosymptomatic disorder for a long time. However, recent research has found that, in addition to tremor, several other motor (e.g., gait

disorder, disturbance of balance [27]) and nonmotor symptoms (e.g., depression, apathy, and anxiety [28]) may also appear in ET.

The clinical diagnosis of ET is based on the careful evaluation of historical data and symptoms [29, 30]. Additional procedures (e.g., tremorometry, electromyography, brain imaging, and laboratory tests) are mainly helpful in the differential diagnosis of tremor.

At present, ET is incurable. The main aims of the symptomatic treatment are the alleviation of tremor interfering with activities of daily living [31] and the improvement of the HRQoL. Treatments for ET include oral medications and device-aided therapies that can be combined if necessary [32, 33].

1.3. Problem statement

Although diagnostic and therapeutic procedures for movement disorders have undergone a huge development during the last few decades, some problems that have long been known and can have a serious impact on the HRQoL are still unsolved. These include that clinical practice uses some drugs known to induce movement disorders not carefully enough and cases with drug-induced movement disorders are often recognized and treated later than optimal. Regarding parkinsonism due to trimetazidine (TMZ), our knowledge of clinical features, and the exact role of diagnostic and therapeutic procedures is limited which prevents clinicians from resolving a clinically relevant problem.

Currently, several scales are available in the field of movement disorders for both clinical and research purposes. To choose the most suitable measures for our aims, in-depth knowledge of the clinimetric properties of available tools is necessary, therefore, systematic testing of scales is of great importance. Regarding newer scales, some fields of applicability with previously established ”gold standards” are often not examined, however, the comparison of old and new tools in certain fields of applicability can have clinical relevance.

Another problem regarding measurement scales is that the minimal clinically important difference (MCID) threshold values have not yet been established for several tools. Without these values, the reliable judgment of findings reported by studies that used these scales as their outcomes is not possible because the results of these trials can be evaluated by statistical methods only and statistical significance does not necessarily imply clinical relevance.

2. AIMS

The primary aims of my research activity were as follows:

- Although diagnosis, differential diagnosis, and treatment of parkinsonism associated with antipsychotic drugs have been thoroughly investigated [22, 34-36], very few studies have been conducted on parkinsonism related to trimetazidine treatment. However, different drugs can cause highly variable clinical features [13]. Therefore, my prospective study aimed to systematically investigate parkinsonism observed during trimetazidine use with a special focus on clinical features, diagnostic tools, and therapeutic options that have not previously been studied, and the health-related quality of life (**Chapter 3**).
- To help the integration of the Parkinson's Disease Composite Scale, a new tool for measuring parkinsonian symptoms, into clinical practice, I aimed to investigate the responsiveness of this scale to an acute levodopa challenge (**Chapter 4)**.
- The minimal clinically important difference threshold values for the Quality of Life in Essential Tremor Questionnaire, a tool used for the measurement of health-related quality of life of patients with essential tremor, have not been established thus far. Without these values, the judgment of the clinical relevance of the results reported by previous studies that used this scale is not possible. Therefore, I aimed to determine the minimal clinically important difference thresholds for the Quality of Life in Essential Tremor Questionnaire (**Chapter 5**).

Because there were significant differences among my studies in the characteristics of the study populations and the methods, I present my trials in three separate chapters.

3. SYSTEMATIC INVESTIGATION OF PARKINSONISM OCCURRING DURING TRIMETAZIDINE TREATMENT

TMZ (1-[2,3,4-trimethoxybenzyl]-piperazine) has been available since the 1970s and widely used as an antianginal drug [37, 38]. According to recent guidelines, TMZ is an efficacious second-line therapeutic option for the treatment of patients with chronic coronary syndrome who are inadequately controlled by or intolerant to first-line antianginal drugs such as beta blockers and calcium channel blockers (recommendation class IIb, level of evidence B) [39].

In addition to gastrointestinal and hematologic side effects of the drug [40], neurological adverse effects developing during TMZ treatment have also been observed. Several studies have reported that TMZ can induce movement disorders (e.g., reversible parkinsonism, tremor, orofacial dyskinesia, gait disturbances, and chorea) and worsen the symptoms of PD [41-46]. Because of the growing number of reported cases of TMZ-related movement disorders, the European Medicines Agency (EMA) reviewed the benefits and risks of TMZ treatment and released a warning on neurological adverse effects of TMZ and a recommendation against the use of this drug in patients with PD in 2012 [47].

Despite previously published data and the recommendation given by the EMA, movement disorders induced or worsened by TMZ still seem to be unsolved problems in clinical practice [48]. A possible reason for this may be the low number of systematic investigations on TMZ-related movement disorders conducted since the first reports.

3.1. Aims

The aims of the present study were:

1.) an in-depth systematic investigation of parkinsonism observed during TMZ use;

2.) the judgment of our hypothesis – based on the results published by Marti Masso et al. [42] and data reported by the EMA [49] – that, on the one hand, TMZ can induce reversible parkinsonism and, on the other hand, it can unmask subclinical PD;

3.) and the identification of tools useful for the differential diagnosis of parkinsonism occurring during TMZ treatment.

3.2. Materials and methods

In this prospective study, consecutive patients were enrolled who presented with previously unrecognized parkinsonism according to the definition of the International Parkinson's Disease and Movement Disorder Society [1] and were on TMZ. Other specific causes for parkinsonism (e.g., specific abnormalities on brain MRI; the use of other dopamine receptor blocking agents; and previous encephalitis, stroke, or serious head trauma) were exclusion criteria. The study was approved by the Regional and Institutional Ethical Committee (3617.316-24987/KK41).

All included patients were managed following a protocol established based on the EMA recommendation [47]. At baseline, sociodemographic-, medication- and disease-related data were recorded, and patients underwent detailed neurological and neuropsychological

examinations. In addition, TMZ was withdrawn and brain MR was performed in all cases. Furthermore, a DaTSCAN examination was also offered for every patient.

Enrolled patients were reassessed 1 month after the withdrawal of TMZ. In those cases where the parkinsonian symptoms improved but did not completely resolve at the 1-month follow-up, another follow-up visit was performed 4 months after TMZ discontinuation. If the parkinsonian features completely disappeared at the 1-month or 4-month visit, the patient was diagnosed with reversible TMZ-induced parkinsonism. If parkinsonian symptoms were present 4 months after the withdrawal of TMZ, we looked for another cause for parkinsonism (e.g., PD). If the diagnosis of PD could be established based on the UK Brain Bank criteria [5], antiparkinsonian treatment was initiated. All patients were re-evaluated one year after the baseline examinations to confirm the previously established diagnoses.

Independent samples t-tests and chi-squared tests were used for comparing clinical data of patients with reversible parkinsonism and PD. The level of statistical significance was set at 5%. The IBM SPSS software package (version 24.0.2, IBM Inc, Armonk, NY, USA) was used for all statistical analyses.

3.3. Results

Data of 33 patients (14 females, mean age: 70.7 ± 6.6 years) were finally analyzed. The duration of TMZ use varied between 18-120 months at baseline. The average time between the onset of parkinsonian symptoms and the baseline examination was 9.7 ± 5.2 months.

At the 1-year follow-up, 11 patients (33.3%) had no parkinsonian symptoms (cases with reversible TMZ-induced parkinsonism). The parkinsonian symptoms improved but did not completely disappear (nonreversible parkinsonism) in 22 patients (66.7%). In these cases, the diagnosis of PD could be established, therefore, antiparkinsonian treatment was initiated.

According to the baseline examinations, less pronounced tremor (tremor scores: 1.5 ± 2.2 vs. 7.7 ± 4.6 points, $p = 0.000$) and more severe rigidity, bradykinesia, postural instability, and gait disturbances (postural instability and gait disturbances scores: 5.3 ± 3.8 vs. 2.0 ± 1.6 points, $p = 0.006$) were observed in patients with reversible parkinsonism. Symptoms of reversible TMZ-induced parkinsonism were more symmetrical (asymmetry index: 3.1% ± 3.6% vs. 40.1% ± 22.2%, $p < 0{,}001$) and milder [Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III scores: 10.5 ± 19.0 vs. 30.5 ± 11.3 points, $p = 0.040$] compared to those of nonreversible parkinsonism. With the exemption of cardiovascular problems, there was no significant difference in the severity of nonmotor symptoms between the two groups. Anxiety and apathy were found to be the most common nonmotor symptoms of reversible TMZ-induced parkinsonism. According to the summary index of the 39-item Parkinson's Disease Questionnaire (PDQ-39), reversible parkinsonism was associated with worse HRQoL compared to nonreversible parkinsonism (**Table 3.1**).

Twenty of 33 patients (7 patients with reversible parkinsonism and 13 patients with nonreversible parkinsonism) underwent DaTSCAN imaging. The result was normal in every patient with TMZ-induced reversible parkinsonism, while all patients with nonreversible parkinsonism had abnormal results.

Table 3.1. Sociodemographic and disease-specific data of patients with reversible and nonreversible parkinsonism at baseline

		Reversibility of parkinsonism		p-value
		Yes (n = 11)	No (n = 22)	
Sociodemographic data				
Age (years)		68.4 ± 4.8	71.8 ± 7.2	0.248[b]
Sex (M/F)		4/7	15/7	0.081[c]
Handedness (R/L)		10/1	21/1	0.606[c]
Education (years)		12.7 ± 2.9	12.1 ± 3.2	0.665[b]
Duration of TMZ use (months)		48.5 ± 20.3	50.7 ± 16.5	0.386[b]
Motor symptoms				
MDS-UPDRS Part II		10.4 ± 6.1	8.2 ± 6.0	0.375[b]
MDS-UPDRS Part II severity[a]	**Mild** **Moderate** **Severe**	6 (54.5%) 5 (45.5%) 0 (0.0%)	18 (81.8%) 4 (18.2%) 0 (0.0%)	0.097[c]
MDS-UPDRS Part III		22.6 ± 10.5	30.5 ± 11.3	0.040[b]
MDS-UPDRS Part III severity[a]	**Mild** **Moderate** **Severe**	10 (90.9%) 1 (9.1%) 0 (0.0%)	12 (54.5%) 10 (45.5%) 0 (0.0%)	0.037[c]
MDS-UPDRS Part IV		4,0 ± 0,8	4,0 ± 1,2	0.836[b]
MDS-UPDRS Part IV severity[a]	**Mild** **Moderate** **Severe**	9 (81.8%) 2 (18.2%) 0 (0.0%)	17 (77.3%) 5 (22.7%) 0 (0.0%)	0.763[c]
Asymmetry index		3.1% ± 3.6%	40.1% ± 22.2%	< 0.001[b]
Tremor score		1.5 ± 2.2	7.7 ± 4.6	< 0.001[b]
PIGD score		5.3 ± 3.8	2.0 ± 1.6	0.006[b]
Nonmotor symptoms				
MDS-UPDRS Part I		12.3 ± 5.0	11.6 ± 5.2	0.585[b]
MDS-UPDRS Part I severity[a]	**Mild** **Moderate** **Severe**	4 (36.4%) 7 (63.6%) 0 (0.0%)	10 (45.5%) 11 (50.0%) 1 (4.5%)	0.640[c]
Lille Apathy Rating Scale		-20.6 ± 6.5	-24.9 ± 5.1	0.058[b]
MADRS		12.9 ± 5.9	10.5 ± 6.4	0.248[b]
Parkinson Anxiety Scale		13.6 ± 7.0	13.0 ± 6.6	0.560[b]
Montreal Cognitive Assessment		21.9 ± 5.1	22.2 ± 3.8	0.977[b]
NMSS				
Cardiovascular problems		6.0 ± 5.0	1.9 ± 2.7	0.021[b]
Sleep problems		8.1 ± 7.9	13.4 ± 10.6	0.178[b]
Mood problems		17.0 ± 14.7	14.0 ± 17.3	0.317[b]
Hallucinations		1.8 ± 5.4	0.8 ± 2.4	0.836[b]
Memory problems		4.7 ± 8.6	5.4 ± 6.3	0.721[b]
Gastrointestinal problems		3.3 ± 4.3	2.5 ± 4.5	0.440[b]
Urinary problems		11.1 ± 8.4	10.4 ± 9.4	0.749[b]
Sexual problems		0.0 ± 0.0	0.5 ± 1.4	0.534[b]
Miscellaneous		2.2 ± 3.7	2.5 ± 4.7	0.985[b]
Total score		54.2 ± 42.2	51.4 ± 43.0	0.510[b]

Table 3.1. Sociodemographic and disease-specific data of patients with reversible and nonreversible parkinsonism at baseline (continued)

	Reversibility of parkinsonism		p-value
	Yes (n = 11)	No (n = 22)	
Health-related quality of life			
PDQ-39			
Mobility	37.7 ± 26.1	9.2 ± 9.1	0.003[b]
Activities of daily living	15.9 ± 14.6	5.9 ± 9.1	0.097[b]
Emotional well-being	24.6 ± 11.4	18.9 ± 15.9	0.063[b]
Stigma	9,1 ± 19.2	1.7 ± 4.4	0.355[b]
Social support	10.6 ± 11.8	7.2 ± 9.0	0.510[b]
Cognition	20.5 ± 12.5	15.0 ± 11.0	0.233[b]
Communication	8.3 ± 15.4	5.3 ± 8.4	0.895[b]
Bodily discomfort	25.0 ± 23.9	25.0 ± 19.6	0.807[b]
Summary index	18.7 ± 9.8	11.1 ± 7.7	0.021[b]

Data are mean ± standard deviation or n (%) unless otherwise indicated.
[a]MDS-UPDRS cut-off values between mild/moderate and moderate/severe levels are the following: Part I: 10.5 points and 21.5 points; Part II: 12.5 points and 29.5 points; Part III: 32.5 points and 58.5 points; Part IV: 4.5 points and 12.5 points [50].
[b]Independent samples t-test
[c]Chi-squared test
Abbreviations: M/F = male/female; **MADRS** = Montgomery-Asberg Depression Rating Scale; **MDS-UPDRS** = Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; **NMMS** = Non-Motor Symptoms Scale; **PDQ-39** = 39-item Parkinson's Disease Questionnaire; **PIGD** = postural instability and gait difficulty; **R/L** = right/left; **TMZ** = trimetazidine

3.4. Discussion

In this prospective study, we systematically analyzed parkinsonism related to TMZ use during long-term follow-up and provided detailed phenomenological and neuropsychological descriptions. We proved that, in some cases, TMZ can worsen subclinical PD, therefore, parkinsonism persisting after TMZ withdrawal may indicate incipient PD. Furthermore, we identified tools that are useful in distinguishing reversible and neurodegenerative parkinsonism because treatments of these disorders are different. Our study also proved that, in addition to the careful evaluation of motor symptoms, DaTSCAN examination seems to be helpful in the differential diagnosis of parkinsonism developing during TMZ treatment. TMZ-induced reversible parkinsonism is characterized by symmetrical rigidity and bradykinesia rather than tremors and a normal DaTSCAN exam can also support a diagnosis of reversible TMZ-induced parkinsonism. However, follow-up of patients is important because it provides a good opportunity for the more careful evaluation of remission of the parkinsonian symptoms and the need for antiparkinsonian treatment. The most remarkable finding of our study was that although motor symptoms of reversible TMZ-induced parkinsonism are generally mild, they can have serious consequences on the HRQoL. Discontinuation of TMZ generally leads to the complete disappearance of symptoms and normalizes quality of life in these cases. The protocol and the results of our study may provide guidance on the management of patients with parkinsonism occurring during TMZ use in everyday clinical practice.

This study was published in Parkinsonism and Related Disorders (Clinical Neurology, Q1, impact factor 2018: 4.360).

4. INVESTIGATION OF THE APPLICABILITY OF THE PARKINSON'S DISEASE COMPOSITE SCALE DURING ACUTE LEVODOPA CHALLENGE

PD is associated with numerous and quite heterogeneous symptoms [5-8], therefore, there is a high need from both clinical and research perspectives to comprehensively assess these problems. Because there was no single validated, reliable, responsive and timely assessable tool that can holistically measure the main motor and nonmotor symptoms of PD and suitable for both everyday clinical practice and research purposes, the European Parkinson's Disease Association sponsored the development of the Parkinson's Disease Composite Scale (PDCS) [51].

The validation studies on the PDCS have found that this new scale seems to be feasible, acceptable, reproducible, valid, and precise [52, 53], however, some of its potential scopes have not yet been studied.

4.1. Aims

The present study aimed to investigate the responsiveness of the PDCS to an acute levodopa challenge and to determine the level of improvement in the PDCS motor score that indicates clinically relevant levodopa response.

4.2. Materials and methods

With the approval of the Regional and Institutional Ethical Committee (3617.316-24987/KK41), we enrolled a consecutive series of patients with parkinsonism [1], undergoing an acute levodopa challenge at our department. The aims of the acute dopaminergic challenge were the differential diagnosis of parkinsonian syndromes or the evaluation of the feasibility of patients for DBS.

During levodopa challenge, first, we assessed the motor sections of the MDS-UPDRS and the PDCS at least 12 hours after antiparkinsonian treatment discontinuation in previously treated patients and prior to the initiation of any antiparkinsonian medication in drug-naïve patients (OFF state). These instruments were reassessed in ON state after the administration of 200-400 mg immediate-release formulation of levodopa/benserazide pills. In those patients, who had chronically been treated previously with antiparkinsonian medications, if it was necessary, further 50-100 mg levodopa was administered, and this dose was repeated until the best ON state was achieved. The acute levodopa challenge was considered as positive if at least 24,5% improvement was documented on the motor part of the MDS-UPDRS [54].

To determine the responsiveness of the PDCS to an acute levodopa challenge, Spearman's rank correlation coefficients were calculated analyzing the association between MDS-UPDRS and PDCS motor changes due to the challenge. In addition, receiver operating characteristic (ROC) analysis was performed to determine the improvements in the PDCS motor score corresponding to 20%, 24.5%, and 30% improvements in the MDS-UPDRS motor score [54, 55]. The Youden method was used to calculate the best cut-off values with the most optimal sensitivity and specificity [56]. The level of statistical significance was set at 0.01. The IBM SPSS software package (version 24.0.2, IBM Inc, Armonk, NY, USA) was used for all statistical calculations.

4.3. Results

A total of 100 patients (47 females, mean age: 66.0 ± 9.7 years) were finally included. The mean duration of disease was 4.7 ± 4.5 years. Forty-nine patients had mild [Hoehn-Yahr stage (HYS) 1&2] parkinsonism, while 23 and 28 patients suffered from moderate (HYS 3) and severe (HYS 4&5) parkinsonism, respectively.

The levodopa test was positive in 83 cases (24 patients with tremor dominant PD, 25 subjects with rigid-akinetic PD, and 24 patients with mixed PD), while negative results indicated other parkinsonian syndromes responsible for the symptoms in 17 patients. Mean MDS-UPDRS and PDCS motor scores were 45.1 ± 15.3 and 13.7 ± 6.2 points in OFF, and 33.2 ± 15.2 and 10.1 ± 6.5 points in ON state, respectively. According to these data, MDS-UPDRS and PDCS motor scores improved by an average of 11.9 ± 10.1 points (27.0 ± 20.1%) and 3.6 ± 4.0 points (28.7 ± 30.3%), respectively, due to the administration of levodopa. Changes in the motor scores of the MDS-UPDRS and the PDCS occurring during an acute levodopa challenge by disease type are shown in **Table 4.1.**

Table 4.1. Average changes in the motor scores of the Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale and the Parkinson's Disease Composite Scale during acute levodopa challenge by disease type

	Disease type			
	Tremor-dominant PD	**Rigid-akinetic PD**	**Mixed PD**	**Other parkinsonism**
MDS-UPDRS OFF[a] (points)	45.3 ± 15.3	43.3 ± 16.5	48.3 ± 15.4	44.3 ± 13.1
MDS-UPDRS ON[b] (points)	31.3 ± 13.5	29.6 ± 17.0	35.3 ± 13.9	40.5 ± 13.5
MDS-UPDRS change (points)	-14.0 ± 10.6	-13.7 ± 10.3	-13.1 ± 10.5	-3.8 ± 2.4
MDS-UPDRS change (%)	-29.7 ± 20.6	-33.5 ± 21.6	-26.9 ± 16.7	-9.9 ± 8.3
PDCS OFF[a] (points)	12.0 ± 5.8	14.0 ± 6.8	14.2 ± 5.7	14.8 ± 6.0
PDCS ON[b] (points)	8.0 ± 5.4	8.8 ± 7.0	11.3 ± 5.8	14.1 ± 6.0
PDCS change (points)	-4.0 ± 3.8	-5.2 ± 4.7	-2.9 ± 3.2	-0.7 ± 1.0
PDCS change (%)	-33.0 ± 28.0	-42.0 ± 34.7	-21.6 ± 24.5	-5.6 ± 8.2
Correlation[c]	0.806 ($p < 0.001$)	0.776 ($p < 0.001$)	0.685 ($p < 0.001$)	0.465 ($p < 0.001$)

Values are mean ± standard deviation.
[a]Antiparkinsonian medications were discontinued at least 12 hours prior to the acute levodopa challenge.
[b]These scores were assessed 60 minutes after a single dose of 200-400 mg immediate-release formulation of levodopa/benserazide or in the best ON state.
[c]Spearman's rho between the relative changes in the motor scores of the Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale and the Parkinson's Disease Composite Scale
Abbreviations: MDS-UPDRS = Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; **PDCS** = Parkinson's Disease Composite Scale; **PK** = Parkinson's disease

High level of correlation (Spearman's rho = 0.726, $p < 0.001$) was found between the relative changes in the MDS-UPDRS and PDCS motor scores. The level of correlation varied according to disease type from 0.465 (non-PD group) to 0.806 (tremor dominant PD, **Table 4.1**).

The area under the ROC curve (AUC) for the change in PDCS motor score corresponding to the clinically relevant 20% improvement in the motor part of the MDS-

UPDRS was 0.883 ($p < 0.001$). The ROC curve AUCs for the improvements in the PDCS motor score corresponding to the 24.5% and 30% changes in the motor examination part of the MDS-UPDRS were 0.885 ($p < 0.001$) and 0.883 ($p < 0.001$), respectively.

The cut-off values for improvements in the PDCS motor score that indicate a clinically relevant response to an acute levodopa challenge with the most optimal sensitivity and specificity and correspond to the 20%, 24.5%, and 30% changes in the motor part of the MDS-UPDRS, were 14.6%, 16.6%, and 18.5%, respectively (**Table 4.2**).

Table 4.2. Corresponding changes in the motor scores of the Parkinson's Disease Composite Scale to the clinically relevant 20%, 24.5%, and 30% improvements in the motor part of the Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale[a]

	PDCS improvement	Sensitivity	Specificity	Youden's index	LR+	LR-	AUC	ROC p-value
MDS-UPDRS 30% improvement	18.47%	0.811	0.894	0.705	7.626	0.211	0.883	< 0.001
MDS-UPDRS 24.5% improvement	16.59%	0.857	0.863	0.720	6.245	0.166	0.885	< 0.001
MDS-UPDRS 20% improvement	14.64%	0.830	0.872	0.703	6.503	0.195	0.883	< 0.001

[a]The cut-off values in the motor score of the Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale were proposed as benchmarks based on references 54 and 55.
Abbreviations: AUC = area under the curve; **LR+** = positive likelihood ratio; **LR-** = negative likelihood ratio; **MDS-UPDRS** = Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; **PDCS** = Parkinson's Disease Composite Scale; **ROC** = receiver operating characteristic analysis

4.4. Discussion

Ideally, a clinical scale should adequately detect the improvement in motor symptoms and differentiate the responders from the nonresponders. At present, the motor examination parts of the Unified Parkinson's Disease Rating Scale and the MDS-UPDRS are the standard tools for measuring the improvement of parkinsonian motor symptoms developing due to the administration of a single dose of levodopa. Considering the definitions of the clinically relevant response to acute levodopa challenge [54, 55, 57], this is the first study that investigated the responsiveness of the motor domain of the PDCS to clinical change during an acute levodopa challenge. Our results show that the PDCS can adequately and reliably respond to an acute levodopa challenge. Any improvement in the PDCS motor scores exceeding the 14.6-18.5% threshold can represent a clinically relevant response to levodopa.

We used a range of improvement in the MDS-UPDRS motor scores indicating a clinically relevant response to levodopa for the identification of a range of variation in the PDCS motor scores demonstrating good levodopa response. In addition, our study population also included patients with non-PD parkinsonism. These may provide the wider and more convenient applicability of our results because they are less dependent on the characteristics of the investigated patient population and, therefore, should not be newly calculated for each study in which they are planned to be used. Our calculations may be helpful for centers that plan to integrate the use of the PDCS motor section into their protocols for performing acute levodopa challenge.

This study was published in Parkinson's Disease (Clinical Neurology, Q2, impact factor 2018: 2.051).

5. THE MEASUREMENT OF THE CLINICAL RELEVANCE OF CHANGES IN QUALITY OF LIFE DUE TO TREATMENTS FOR ESSENTIAL TREMOR

Measuring deterioration and improvement in the HRQoL has become a standard approach for evaluating disease progression and treatment outcomes [58, 59]. A growing body of research data shows that ET can have a deleterious impact on the activities of daily living and, as a result, it can also greatly impair the HRQoL [31, 60, 61]. Therefore, recent studies on the treatments for ET have put a special focus on the investigation of the effects of ET on the HRQoL and activities of daily living [62, 63]. The standard evaluation tool of the HRQoL in ET is the Quality of Life in Essential Tremor Questionnaire (QUEST) [64].

Although the QUEST has been widely used in clinical research [65-67], changes in its summary index can be evaluated by statistical methods only at present because the MCID threshold values for this instrument have not been established yet. However, statistical significance does not necessarily indicate clinical relevance [68]. MCID values help the judgment of statistically significant results on their clinical relevance. These thresholds reflect the smallest changes in an outcome measure that are perceived and considered as meaningful by both the patients and the clinicians [69].

5.1. Aims

The present study aimed to determine the MCID thresholds for the summary index of the QUEST and, using the calculated MCID values, to judge the findings of previous studies that have investigated available treatments for ET on their clinical relevance.

5.2. Materials and methods

With the approval of the Regional and Institutional Ethical Committee (3617.316-24987/KK41), we enrolled patients with ET who were treated in our center and gave their informed consent for participating in the study.

The QUEST was assessed both during the baseline and follow-up visits. In addition to the reassessment of the QUEST, patients were asked to rate the perceived changes in ET-related difficulties since the last visit on the Patient-rated Global Impression – Improvement (PGI-I) [70] at the follow-up visits.

As it has been recommended by Revicki et al. [71], the MCID thresholds for the QUEST were calculated using anchor- (measurement of the change in a patient-reported outcome, sensitivity- and specificity-based approach) and distribution-based (ROC analysis) methods simultaneously [69, 71-73]. In the present study, the PGI-I was selected for being an anchor. Based on the results of the Spearman's correlation method and ordinal regression modeling, this instrument was capable of being an anchor [71].

MCID values for the summary index of the QUEST were calculated both independently from and specifically for the severity of disease (mild: $\leq$ 11.25, moderate: 11.26-20.35, and severe > 20.35, based on the summary index of the QUEST [74]) to increase the reliability and applicability of our thresholds. All statistical analyses were performed using the IBM SPSS software package (version 24.0.2, IBM Inc., Armonk, NY, USA).

5.3. Results

895 paired examinations of 248 patients with ET (mean age: 58.7 ± 16.7 years, mean duration of disease: 11.8 ± 11.3 years) were analyzed. Twenty-one investigations were excluded because of incompletely answered questionnaires. The median number of follow-up visits was 3 (interquartile range: 2-7) with a median inter-visit interval of 6 months (interquartile range: 3-12 months).

Threshold values for minimal yet clinically meaningful improvement and worsening in the summary index of the QUEST could be set at 4.47% and 4.98%, respectively (**Table 5.1**). MCID values calculated based on disease severity can be seen in **Table 5.2**.

Table 5.1. Minimal clinically important difference threshold values for the summary index of the Quality of Life in Essential Tremor Questionnaire

	PGI-I[a]	Number of paired visits	Change (follow-up vs. baseline)			Effect size (Cohen's d)	ROC analysis		
			Mean ± SD	95% CI			Optimal cut-off	Sensitivity	Specificity
QUEST SI	3	157	-4.47 ± 3.21	-5.11	-1.75	0.23	-4.47	0.725	0.824
	4	274	-0.05 ± 2.91	-1.02	1.19	0.01		-	
	5	124	4.98 ± 3.47	1.07	6.37	0.19	4.98	0.817	0.793

[a]Values for the Patient-rated Global Impression – Improvement are the following: 3 = a little better, 4 = the same, 5 = a little worse.
Abbreviations: CI = confidence interval; **PGI-I** = Patient-rated Global Impression – Improvement; **QUEST SI** = summary index of the Quality of Life in Essential Tremor Questionnaire; **ROC** =receiver operating characteristic; **SD** = standard deviation

Table 5.2. Minimal clinically important difference threshold values for the summary index of the Quality of Life in Essential Tremor Questionnaire calculated specifically for disease severity

	PGI-I		Disease severity[a]			Overall
			Mild	Moderate	Severe	
QUEST SI	3	a little better	-4.11	-4.53	-4.59	-4.47
	4	the same	-0.12	-0.01	0.02	-0.05
	5	a little worse	5.11	4.78	4.89	4.98

[a]Threshold values for disease severity published in the reference 74 were used for categorization.
Abbreviations: PGI-I = Patient-rated Global Impression – Improvement; **QUEST SI** = summary index of the Quality of Life in Essential Tremor Questionnaire

In a Pubmed search conducted in December 2019, we identified 16 studies investigating treatments for ET and reporting changes in the summary index of the QUEST as their outcomes. Of them, 1 study evaluated pharmaceutical treatments for ET [65], 5 trials were conducted on botulinum neurotoxin [67, 75-78], 9 studies examined functional neurosurgical treatments for ET [62, 63, 66, 79-84], and 1 study was published on the efficacy of other treatments [85]. Considering our MCID estimates, botulinum neurotoxin, DBS, and MR-guided focused ultrasound thalamotomy can improve the HRQoL in ET in a clinically relevant manner.

5.4. Discussion

The concept of MCID is increasingly used in biomedical research to decide whether statistical significance implies clinical relevance. Several studies investigating treatments for ET have been reported the summary index of the QUEST as their outcomes, however, the clinical relevance of these findings could not be evaluated because no MCID threshold values for the summary index of the QUEST were available.

For the calculation of the MCID values for the summary index of the QUEST, we simultaneously used anchor- and distribution-based methods resulting in similar MCID estimations. Based on our results, any improvement greater than 4.47% and any worsening exceeding 4.98% are clinically meaningful changes in the summary index of the QUEST. Regarding sociodemographic and disease-specific characteristics (e.g., duration and severity of disease), we used a heterogeneous study population to calculate these values. However, taking into account the dependency of MCID values on the characteristics of the study population [86], we performed further analyses to determine cut-off values specific for disease severity [74]. The heterogeneous study population and MCID thresholds calculated specifically for disease severity ensure the reliability and wider applicability of our results, therefore, our values should not be newly calculated for future studies. Our MCID estimations may be a good base for the planning of clinical studies, calculating sample power, and judging the outcomes of clinical trials.

This study was published in Movement Disorders (Clinical Neurology, D1, impact factor 2018: 8.061).

7. SUMMARY OF NOVEL FINDINGS

The novel findings of my doctoral research activity are the following:

- In a prospective study, in addition to the detailed description of the motor features of reversible trimetazidine-induced parkinsonism, we also explored the nonmotor symptomatology of the disease that was mainly characterized by anxiety and apathy. We found that reversible trimetazidine-induced parkinsonism can drastically impair the health-related quality of life. We also proved that, in some cases, trimetazidine may worsen the symptoms of subclinical Parkinson's disease and, as a result, unmask the disorder. Furthermore, we identified some tools that are useful in the differential diagnosis of parkinsonism occurring during trimetazidine use. The careful evaluation of the motor symptoms (e.g., evaluation of symmetry of symptoms, examination of gait and postural stability), DaTSCAN examination, and follow-up of patients seem to be helpful in distinguishing reversible and neurodegenerative parkinsonism. The methods and results of our study may provide guidance on the management of patients with parkinsonism occurring during TMZ use and contribute to the resolution of this clinically relevant problem.
- To help the clinimetric validation of the Parkinson's Disease Composite Scale, we proved that the motor part of this instrument can adequately and reliably respond to an acute levodopa challenge. We also determined a range of improvement (14.6-18.5%) in the motor score of the scale that indicates a clinically relevant levodopa response. Our findings may be helpful for centers that plan to integrate the use of this tool into their protocols for performing acute levodopa challenge.
- We determined the minimal clinically important difference thresholds for the Quality of Life in Essential Tremor Questionnaire both independently from and specifically for the severity of disease. Based on our estimations, any improvement greater than 4.47% or any worsening exceeding 4.98% are clinically meaningful changes in the summary index of this tool. Minimal clinically important difference values for improvement and worsening were -4.11%, -4.53%, and -4.59% and 5.11%, 4.78%, and 4.89% in mild, moderate, and severe essential tremor, respectively. Our findings may be helpful in the judgment of the results of previous studies and the planning of future trials.

8. FUTURE AIMS

Building on the results that have been achieved thus far, my future aims are as follows:

- I would like to prove the clinical applicability of the methods introduced in **Chapter 3.** In addition, to evaluate the symptomatic improvements resulting from the discontinuation of TMZ on their clinical relevance, I would like to determine the level of change in the severity of parkinsonian symptoms and the HRQoL using scales that are widely applied in both the national and international clinical practice (e.g., MDS-UPDRS, PDQ-39). Furthermore, I would like to evaluate the impact of the EMA recommendation on the use of TMZ in the population with PD in Hungary by analyzing data from the database of the National Health Insurance Fund of Hungary.
- At present, several scales are available for measuring the severity of tremor in parkinsonism (e.g., Fahn-Tolosa-Marin Tremor Rating Scale [87], MDS-UPDRS Part III [88], and MDS-UPDRS-based Tremor Scale [89]). Although these scales underwent detailed clinimetric testing, their sensitivity to change due to antitremor treatment has not been evaluated thus far. Because further clinimetric validation could help the more reliable application of these instruments, in relation to the study introduced in **Chapter 4**, I would like to evaluate the sensitivity of the scales used to measure tremor to change resulting from antitremor treatment. My aim is to identify the scale that can measure the efficacy of antitremor treatment most reliably.
- Using the methods introduced in **Chapter 5**, I would like to determine the MCID thresholds for the Burke-Fahn-Marsden Dystonia Rating Scale [90], the Burke-Fahn-Marsden Dystonia Disability Scale [90], and the SF-36 [91]. These scales are widely used in clinical practice and research related to dystonia. Using the calculated MCID values, I would like to evaluate the results of previous studies investigating treatments for dystonia on their clinical relevance.

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PUBLICATIONS

MTMT ID: 10065925

Publications related to PhD training:

	All	First or last authored	Citations	
			All	Independent
Peer-reviewed articles	9	5	4	3
Related to the thesis	3	3	2	1
Q1	2	2	---	---
Of which D1	1	1	---	---
Q2	1	1	---	---
Q3	0	0	---	---
Q4	0	0	---	---
Unrelated to the thesis	6	2	2	2
Q1	2	1	---	---
Q2	1	0	---	---
Q3	0	0	---	---
Q4	1	0	---	---
Scientific presentations	14	6	0	0
Related to the thesis	4	3	0	0
Unrelated to the thesis	10	3	0	0
Scientific posters	6	3	0	0
Related to the thesis	1	1	0	0
Unrelated to the thesis	5	2	0	0
Citable abstracts	6	3	0	0
Related to the thesis	0	0	0	0
Unrelated to the thesis	6	3	0	0
Cumulative impact factor[a]	25.240	18.859	---	---
Cumulative impact factor of articles related to the thesis	14.472	14.472	---	---

[a]Without the cumulative impact factor of citeable abstracts (28.343)

I. Peer-reviewed articles related to the thesis:

Pintér D, Makkos A, Kovács M, Janszky J, Kovács N Minimal Clinically Important Difference for the Quality of Life in Essential Tremor Questionnaire MOVEMENT DISORDERS 34:(5) pp. 759-760., 2 p. (2019)

Neurology (clinical), 11/363 (D1), IF (2018): 8.061

Pintér D, Kovács M, Harmat M, Juhász A, Janszky J, Kovács N Trimetazidine and parkinsonism: a prospective study. PARKINSONISM AND RELATED DISORDERS 62 pp. 117-121., 5 p. (2019)

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All citations: 2 Independent: 1 Dependent: 1

Pintér D, Martinez-Martin P, Janszky J, Kovács N The Parkinson's Disease Composite Scale is adequately responsive to acute levodopa challenge PARKINSON'S DISEASE Paper: 1412984, 8 p. (2019)

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II. Scientific presentations related to the thesis:

Pintér D, Kovács M, Harmat M, Juhász A, Janszky J, Balás I, Kovács N A trimetazidin terápia alatt jelentkező parkinsonizmus klinikai tünettanának szisztematikus vizsgálata. Pécsi Tudományegyetem Idegtudományi Centrum III. PhD és TDK Konferencia, 2018.11.22.-2018.11.23., Pécs.

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IV. Peer-reviewed articles unrelated to the thesis:

Kovács N, Aschermann Zs, ***Pintér D***, Juhász A, Harmat M, Janszky J, Balás I Generalizált disztóniák kezelése mély agyi stimulációval. NEUROLÓGIAI PRAXIS 1:(3) pp. 14-15., 2 p. (2018)

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Makkos A, Kovács M, ***Pintér D***, Janszky J, Kovács N 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)

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All citations: 1 Independent: 1 Dependent: 0

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

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Pintér D, Nagy M, Büki A, Janszky J, Kovács N, Aschermann Zs, Juhász A, Kövér F, Perlaki G, Balás I A mély agyi stimuláció hatása az agyi térfogatra Parkinson-kóros betegeknél. Doktoranduszok a Klinikai Kutatásokban Konferencia, 2017.10.28., Pécs.

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Pintér D, Kovács M, Makkos A, Juhász A, Darnai G, Janszky J, Kovács N Preexisting Diabetes Mellitus Is Associated with More Frequent Depression and Impulse Control Disorders in Drug Naïve Parkinson's Disease. The 14th International Conference on Alzheimer's & Parkinson's Diseases, March 26-31, 2019, Lisbon, Portugal.

Kovács N, Janszky J, ***Pintér D***, Harmat M, Juhász A, Vörös V, Balás I Interleaving stimulation mode can improve better the health-related quality of life in primary generalized or segmental dystonia than standard bilateral pallidal deep brain stimulation. The 14th World Congress of the International Neuromodulation Society, May 25-30, 2019, Sydney, Australia.

Kovács N, Balás I, ***Pintér D***, Juhász A, Harmat M, Vörös V, Janszky J Interleaving stimulation mode can improve better the health-related quality of life in primary generalized or segmental dystonia than standard bilateral pallidal deep brain stimulation. XXIV. World Congress of Neurology, October 27-31, 2019, Dubai, United Arab Emirates.

VI. Scientific posters unrelated to the thesis:

Kovács N, Pál E, ***Pintér D***, Kovács M, Makkos A Repetitive transcranial magnetic stimulation can improve anxiety in Parkinson's disease: a randomized, double-blind and controlled trial. 1st EMF-Med World Conference on Biomedical Applications of Electromagnetic Fields & COST EMF-MED Final Event with 6th MCM, September 10-13, 2018, Split, Croatia.

Pintér D, Kovács M, Makkos A, Juhász A, Darnai G, Janszky J, Kovács N Preexisting Diabetes Mellitus Is Associated with More Frequent Depression and Impulse Control Disorders in Drug Naïve Parkinson's Disease. The 14th International Conference on Alzheimer's & Parkinson's Diseases, March 26-31, 2019, Lisbon, Portugal.

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VII. Citable abstracts unrelated to the thesis:

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Folyóirat szakterülete: Neurology (clinical), helyzete: 126/363 (Q2), IF (2018): 2,651

Kovács N, Balás I, ***Pintér D***, Juhász A, Harmat M, Vörös V, Janszky J Interleaving stimulation mode can improve better the health-related quality of life in primary generalized or segmental dystonia than standard bilateral pallidal deep brain stimulation. JOURNAL OF THE NEUROLOGICAL SCIENCES 405:(Suppl) pp. 30. (2019)
Folyóirat szakterülete: Neurology (clinical), helyzete: 126/363 (Q2), IF (2018): 2,651

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