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Review article

Factors that Impact on Quality of Life of People with Disease with Tremor: Systematic Review

Ricardo Zanetti Gomes [1], Luisa Pereira de Oliveira Zanetti Gomes [*2], Vitória Rossetim Celinski [1], Camila Marinelli Martins [1], Omar El Sayed [1], Letícia Fillos [1], Andrielle Cristina Chaicoski [1]

[1]University State of Ponta Grossa, Ponta Grossa, PR, Brazil
[2]University of the Region of Joinville, Joinville, SC, Brazil

*Corresponding author: Luisa Pereira de Oliveira Zanetti Gomes; *luisazanettigomes@gmail.com*

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Abstract

Background: Parkinson's disease and essential tremor are common diseases that cannot be cured. These diseases cause a major impact on the patients' lifestyle, and as they are progressive over time, their symptoms tend to get worse as well as these individuals' quality of life. Objective: To analyze how the duration of the disease impact quality of life and other aspects related to the disease. Methods: A systematic review was carried out, and a meta-analysis developed including original articles published after 2006 that assessed the quality of life of patients with diseases that presented tremor as a symptom. Results: The number of papers found totaled 7.114, out of those, 27 were included in the systematic review, and 15 of them were also included in the meta-analysis. The articles found analyzed sociodemographic, neuropsychiatric scales, and disease severity scales. In the meta-analysis we found that the time of disease impacts the score of PDQ-39 in numbers of dominants, the mini-mental score, and the UPDRS score. Conclusion: Longer time of disease since diagnostic results in a negative impact on the patients' quality of life, cognition, emotional status, activities of daily living, motor examination, and therapy complication.

Keywords: ***Parkinson's diaseas, essential tremo, quality of life***

Introduction

According to the World Health Organization (WHO), 1% of the global population over 65 years-old has Parkinson's disease. This disorder is the second most prevalent neurodegenerative disease in the world [1]. The pathophysiology of Parkinson's disease is related to dysfunction of the cells responsible to produce dopamine in the substantia nigra and acetylcholine in the pedunculopontine nucleus of the basal ganglia. Alterations in the basal ganglia, and other parts of the brain are associated, and alterations in other neurotransmissions have also been observed [2,3]. Its clinical presentation is characterized by resting tremor, bradykinesia, rigidity, and postural instability [4]. In the early stage of the disease, symptoms can be relieved with dopamine agonists and other drugs, but as the disease progresses adverse effects or refractoriness to treatment may occur [5].

The prevalence of essential tremor is 23.7 per 100.000 (inhabitants). This is not a simple motor disorder, its pathophysiology involves cerebellar Purkinje cell dysfunctions with loss and gliosis, and other alterations in other parts of the brain. The illness has been associated with other alterations like cognitive and mood disorder [6]. It is characterized by the presence of kinectic and postural tremor. With the progression of this disease, the tremor frequency tends to decrease, but its amplitude tends to increase. This fact impacts the patients social life, because it impacts one's ability to perform daily tasks [7].

Both diseases are chronic and degenerative. These disorders result in a number of factors that impact the patients' quality of life such as depression, disability, disease severity, and cognitive impairment [8]. Over time and with the progression of the diseases, an increase in the dependency to perform daily tasks occurs, thus causing a negative impact on the individuals affected.

The aim of this paper is to correlated time since the diagnosis and how this and other factors impact the quality of life of people with essential tremor and Parkinson's disease.

Methodology

The Preferred Reporting Items guidelines for Systematic Reviews and Meta-Analyses (PRISMA) [9] were used to guide this systematic review (PROSPERO registration number: CRD42021221329).

The search was carried out in August 2020 by surveying the PUBMED, LILACS, EBSCO, and the Cochrane Library databases. The descriptors used were "Quality of life OR life quality OR QoL OR Health-related quality of life OR quality of life in Parkinson disease questionnaire OR Whoqol AND Tremor OR essential tremor OR Parkinson disease OR Parkinsonism". Duplicates were removed.

The inclusion criteria were studies with patients diagnosed with pathologies involving tremor, including Parkinson's disease, essential tremor, and parkinsonism that assessed quality of life through a scale. Articles that did not address quality of life or did not relate it to an application of a specific treatment were excluded. Articles published before 2006 were also excluded. The language of publication was not considered as an exclusion criterion.

The articles were selected by 4 previously trained independent reviewers by reading the title and respective abstracts, checking whether they met inclusion or exclusion criteria. Articles that reported studies with potential were read in full and assessed

whether they fit within the focus of the research. In cases of disagreement, a fifth reviewer was called to assist with the decision.

Data extraction from the articles was performed using a table in the Excel program and extracting the following data: Characteristics of the articles, including number of participants, year of publication, and author; demographic characteristics of the population: age, employment status, marital status); age at onset of illness, duration of tremor, reports of anxiety and depression; type of treatment adopted; disease severity scales: Tolosa Marin tremor rating scale, Hoehn and Yahr scale, Updated Parkinson's disease rating scale (UPDRS); neuropsychiatric disease scales: DASS Scale, geriatric depression scale-15 Scale, Hospital Anxiety and Depression Scale, Beck Depression Inventory (BDI); mini mental state examination; and quality of life scales: Parkinson disease questionnaire- 39 (PDQ-39) and Parkinsons disease questionnaire-8 (PDQ-8) , EQ-VAS Scale, EuroQol Index, EQ-5D, and SF-36.

The authors of the studies that presented insufficient data were contacted via email to request these missing data.

Risk of bias

The risk of biases was assessed using the Study Quality Assessment Tools developed by the NHLB [10], which is a compilation of questions that could be answered yes, no or not reported that can be applied to cohort and observation studies. These questions evaluated the study design as well as internal and external validity.

Data analysis

Data were analyzed using meta-analysis models to estimate the influence of time since diagnosis on the severity of tremors and on various aspects of quality of life assessed in the studies. Pooled effects were estimated using the method of weighted inverse variance for continuous outcomes to obtain a combined measure between the evaluated scores. Heterogeneity between studies was tested with the I2 test, considering it significant when $p < 0.05$. The alternative hypothesis of the heterogeneity test is that the variability/heterogeneity is significant, therefore, fixed, or random effects models were chosen based on the acceptance or rejection of the null hypothesis. All analyzes were performed in the R environment (R Core Team, 2019) with the "meta" package (Schwarzer, 2007).

Results

The survey of the databases resulted in 7,114 articles found, 27 out of those were selected for this review (Figure 1). Fifteen studies were included in the metanalysis. These papers assessed quality of life using the PQD-39, EQ-VAS, EQ5D SF36, Nottingham Health Profile, the UPDRS scale, or Mini-mental examination. The groups were subdivided according to time since diagnosis of Parkinson's Disease or Essential tremor, resulting in three subgroups: 5 years, 5.1-10 years, and more than 10 years.

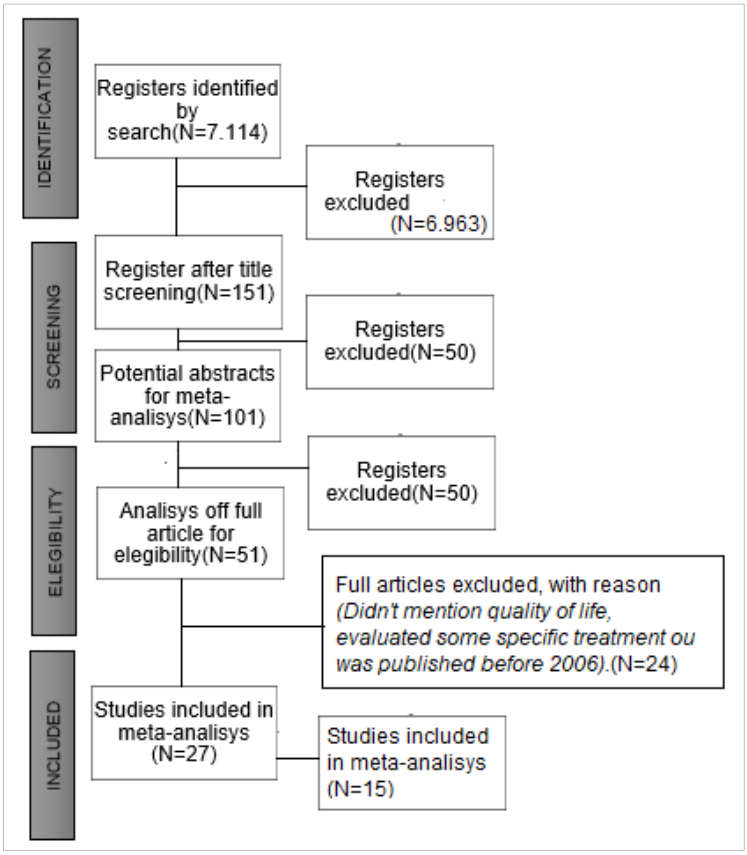

Figure 1: PRISMA Flow Diagram

Quality of life in Parkinson's Disease was assessed in 24/27 (88.88%), while 3/27 (11,11%) investigated quality of life in Essential Tremor (Table 1). The participants' age range was 40-75 years, and the mean age of the participants of most articles was 60 years old.

Table 1: Summarizing study characteristic

Study	Country	Type	Disease	Number of Participan	Quality of Life Scale	Risk of Bias- Yes*	Risk of Bias-No *
Bugalhao,2016[19]	Portugal	Cross-sectional	Parkinson	143	EQ-Index EQ-VAS	58.30%	41.60%
Soh,2013 [44]	Australia	Cross-sectional	Parkinson	210	PDQ-39	50%	50%
Visser, 2008.[23]	Netherlands	Cross-sectional	Parkinson	378	EuroQol-5D Visual Analogue Scale.	66.66%	33.33%

Spadaro, 2013[45]	Italy	ecological	Parkinson	85	PDQ-39	58.33%	41.66%
Soh, 2012 [46]	Australia	Cross-sectional + meta-analysis	Parkinson	210	PDQ-39	41.60%	58.33%
Moreira, 2017.[47]	Brazil	Cross-sectional	Parkinson	100	PDQ-39	58.33%	41.60%
Visser, 2009[22]	Netherlands	longitudinal cohort	Parkinson	336	EuroQol-5D	83.30%	16.60%
Tedrus 2010[20]	Brazil	Cross-sectional	Parkinson	20	PDQ-39	66.60%	33.33%
Bucks,2011[14]	Australia	Cross-sectional	Parkinson	85	PDQ-39	41.60%	58.30%
Winter,2010[16]	Australia	Cross-sectional	Parkinson	81	EuroQol (EQ5D and EQVAS)	53.80%	46.10%
Zhao, 2008[18]	Singapura	Cross-sectional	Parkinson	183	PDQ8	53.80%	46.10%
Carod-Artal, 2007[21]	Brazil	Cross-sectional	Parkinson	144	PDQ39	58.33%	41.60%
Simpson,2014[17]	United Kingdom	Cross-sectional	Parkinson	81	PDq39	75%	25%
Ngo et al, 2019[15]	Vietnam	Cross-sectional	Parkinson	268	PDQ-39	75%	25%
FORSAA et al, 2008[48]	Norway	Cohort	Parkinson	239	Nottingham Health Profile (NHP)	92.30%	7.69%
Chandran,2013[11]	India	Cross-sectional	Essential tremor	50	QUEST	50%	50%
Violante,2013[29]	Mexico	Cross-sectional	Parkinson	177	PDQ-39	50%	50%
WINTER,2010 [49]	Russia	Cross-sectional	Parkinson	100 com PD e 100 controls	EQ-5D and EQ VAS	63.63%	36.36%
LORENZ, 2006[13]	Germany	Cross-sectional	Essential tremor	105	SF36	36.36%	63.63%
Andreadou,2011[27]	Greece	Cross-sectional	Parkinson	139	PDQ-39	58.33%	41.66%
Reuther,2007 [24]	Germany	longitudinal cohort	Parkinson	145	PDQ-38, EQ-5D	50%	50%
Navarro-Peternella, 2012[50]	Brazil	Cross-sectional	Parkinson	40	PDQ-39	69.20%	30.76%
Kahraman, 2018[51]	Turkey	Cross-sectional	Parkinson	83	SF36 and PDQ-8	41.66%	58.33%
Filippin,2015[52]	Brazil	Cross-sectional	Parkinson	10	PDQ-39 and SF36	45.45%	54.54%
Shalash, 2019[12]	Egypt	case control	Essential tremor	60	SF36	66.66%	33.33%
Silva, 2011[53]	Brazil	Cross-sectional	Parkinson	25	PDQ-39	50%	50%

*The answer "YES" corresponds to the presence of the well-defined characteristic in the study. * The answer "NO" corresponds to the absence of the well-defined characteristic in the study.*

Social life and labor factors were analyzed in 12 articles, in most of these studies, the patients lived with someone else, over 70% lived with a partner, and only a few individuals lived with a caregiver, relative, or a friend. The number of unemployed/retired participants was higher than that of working people, comprising 75% of the sample.

The severity of Parkinson's disease was classified by Hoen&Yarh scale in 19 articles. Mild illness was reported in 4 of these studies, the mean score of the participants was 1-2 and moderate illness appeared in 9 of these studies, the mean score of the participants was 2.5-3. Four of these articles subdivided the number of participants according to each Hoen&Yarh subgroup (HYI-n=159, HY2n=508, HYIII, n=233, HYIV n=132, HYV=22, HY2.5=n=32). To assess he essential tremor severity, the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS) was used [11-13].

In Bucks, 2011[14] most of the participants (60%) presented clinically significant anxiety, whose severity was mild or even extremely severe. More than 1/3 of the patients (n = 33) showed related clinically significant depression, but only 10 of them (11.36%) were taking antidepressants or anxiolytics. In Ngo et al, 2019 [15] almost half of the sample (48.2 %) was affected by depression or anxiety. WINTER, 2010 [16] found out depression in 58% of the patients (n=47), according to the ICD-10 criteria. Simpson 2014 [17] reported that 11 individuals were affected by at least moderated depression symptoms.

The Geriatric Depression Scale - 15 (GDS-15) [18], Depression Anxiety Stress Scale (DASS) [14,17], Hospital Anxiety and Depression Scale (HADS) [19-21], and Beck Depression Inventory-BDI [12,22-24] were used in 10 studies to assess neuropsychiatric symptoms. Most patients included were affected by mild or moderate neuropsychiatric illness and in two studies this condition was not identified [17,24].

Seven articles [22-27, 21] reported the treatment adopted by patients, most of them were taking Levodopa (n=1.157). Only a few participants were taking dopamine agonists (n=579). Two studies [24,27] also reported the treatment with both drugs (n=113). Some studies [22,23,28] also described the levodopa dosage, and two articles [16,29] reported the presence of dyskinesia.

The EQ-VAS was used to evaluate 1481 patients, the score ranged from 48 to 62. In the Euro QOF index (n=486), the score ranged between 46 and 49. Two-hundred and thirty-nine individuals were evaluated using the SF-36 scale. The mean score in the NHP scale (n=277) was 197. Fifty individuals were submitted to QUEST and the mean score was 24. The mean score obtained by 144 patients that were evaluated by SCOPA-PS was 39, and 183 individuals were evaluated using the PDQ-8 scale.

In this review, six articles correlated quality of life with age, gender, UPDRS, dementia, marital status, salary, time since diagnosis, work, Hoenh &Yarh scale, and neuropsychiatric disease. Figure 2 represents the correlation of quality of life and depression, time since diagnosis and Hoenh &Yarh scale. Time since diagnosis was evaluated in two articles and the highest correlation was presented. The results of the correlations show that quality of life is reduced by all these factors, with some exceptions such as time correlated with stigma, social life with Hoenh &Yarh, and discomfort over time.

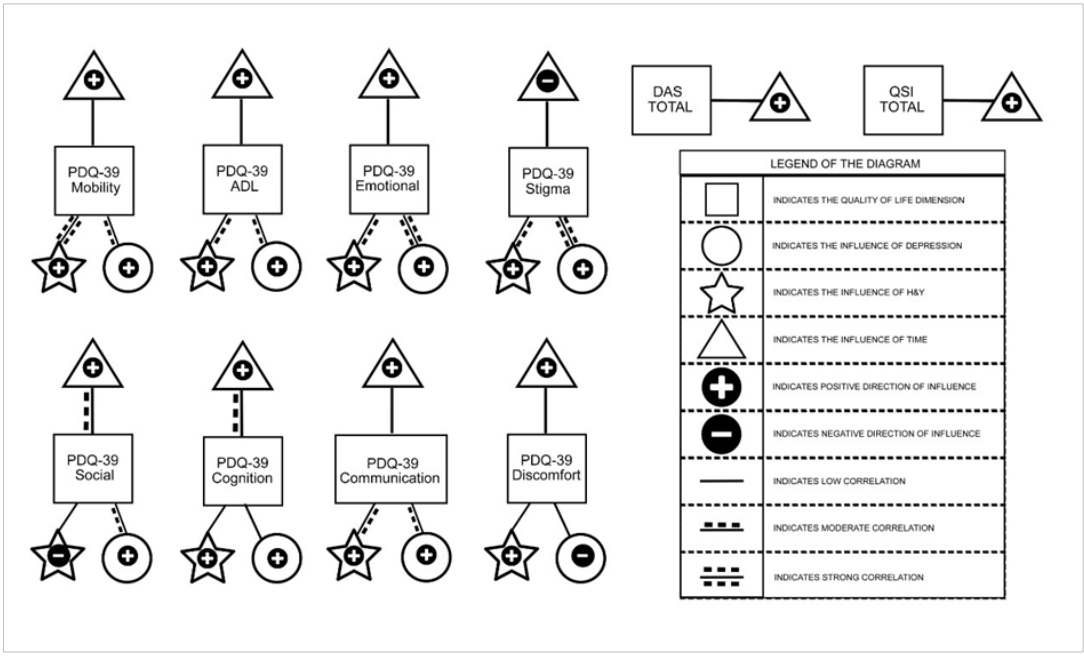

Figure 2: Correlations

PDQ-39- Parkinson's disease questioner 39. DAS- Depression Anxiety Stress Scales QSI-QUEST summary index.

UPDRS I shows that individuals with more than ten years of Parkinson's disease presented worse clinical condition and also a poorer quality of life, when compared to individuals that have the disease for between five and ten years. There is no data about less than five years since diagnosis. The results are statistically significant (Table 2). The heterogeneity of the studies was high.

Table 2: UPDRS And Mini-Mental

	Pooled effect	**CI 95%**	**I^2 and heterogeneity p- value**
UPDRS_I			
General	3.55	2.40 – 4.69	I^2= 98% p<0.01
Duration up to 5 years	*	*	*
Duration 5,1 to 10 years	3.01	2.50 – 3.51	I^2= 82% p<0.01
Duration over 10 years	5.10	4.72 – 5.48	**
UPDRS_II			
General	14.29	11.30 – 17.29	I^2= 97% p<0.01
Duration up to 5 years	*	*	*
Duration 5,1 to 10 years	12.92	11.93 – 13.91	I^2= 71% p<0.01
Duration over 10 years	23.80	22.60 – 25.00	**
UPDRS_III			
General	27.00	21.99 – 32.02	I^2= 99% p<0.01
Duration up to 5 years	18.95	17.42 – 20.48	**
Duration 5,1 to 10 years	26.05	21.48 – 30.61	I^2= 98% p<0.01
Duration over 10 years	44.50	42.23 – 46.77	**
UPDRS_t			
General	48.60	46.47 – 50.73	I^2= 20% p=0.28
Duration up to 5 years	*	*	*
Duration 5,1 to 10 years	48.60	46.47 – 50.73	I^2= 20% p=0.28
Duration over 10 years	*	*	*
Mini-mental			
General	26,15	24,86 – 27,44	I^2= 98% p<0,01
Duration up to 5 years	28,17	27,68 – 28,66	I^2= 77% p=0,04
Duration 5,1 to 10 years	26,75	25,14 – 28,35	I^2= 95% p<0,01
Duration over 10 years	20,40	19,35 – 21,45	**
*There were not studies that evaluated this factor in this condition; ** only 1 study: there was no heterogeneity test			

In UPDRS II, no data about less than five years since diagnosis was found. The comparison between five and ten in years since diagnosis and more than ten years showed statistically significant values. The heterogeneity of the studies was high (I2=97%).

In UPDRS III, we could analyze values from the beginning of the disease and those with over ten years after diagnosis, which enabled a better view of the quality of life, due to a larger sample. The values showed an increasing trend over time and also a deterioration of the quality of life. The results were statistically significant. The heterogeneity of the studies was high (I2=98%).

UPDRS t only presented values for the period five to ten years of the disease duration, therefore, a comparison with other periods of the disease duration was not possible. The heterogeneity of the studies was low (i2=20%).

Mini-mental

The score obtained in the Mini Mental decreased when the time since diagnosis increased (Table 2). The values for the three subgroups were statistically significant and the comparison between groups did not find statistical difference between them. The heterogeneity of the studies was high.

PDQ-39

Studies that used the PDQ-39 scale were included in this meta-analysis and the results are represented in Table 3. In all domains of the scale, all participants deteriorated as the time since diagnosis increased. This is represented by a higher mean score in the scale. The heterogeneity of the studies was high or moderate (i2=41%).

Table 3: PDQ 39

	Pooled effect	IC 95%	I^2 and heterogeneity p-value
Activity of daily living			
General	37.27	31.73 – 42.81	I^2= 93% p<0.01
Duration up to 5 years	26.01	15.36 – 36.67	I^2= 91% p<0.01
Duration 5,1 to 10 years	26.75	35.37 – 44.13	I^2= 87% p<0.01
Duration over 10 years	*	*	*
Emotional			
General	33.85	26.28 – 41.42	I^2= 98% p<0.01
Duration up to 5 years	18.74	12.04 – 25.45	I^2= 84% p=0.01
Duration 5,1 to 10 years	26.75	29.72 – 44.14	I^2= 98% p<0.01
Duration over 10 years	*	*	*
Stigma			
General	21.50	16.25 – 26.75	I^2= 95% p<0.01
Duration up to 5 years	15.08	11.98 – 18.19	I^2= 0% p=0.75
Duration 5,1 to 10 years	22.86	16.80 – 28.91	I^2= 96% p<0.01
Duration over 10 years	*	*	*
Mobility			
General	36.80	31.22 – 42.38	I^2= 93% p<0.01
Duration up to 5 years	23.80	20.21 – 27.39	I^2= 41% p=0.19
Duration 5,1 to 10 years	39.37	34.29 – 44.46	I^2= 90% p<0.01
Duration over 10 years	*	*	*
Social support			
General	16.09	9.76 – 22.43	I^2= 98% p<0.01
Duration up to 5 years	9.23	1.21 – 17.26	I^2= 92% p<0.01
Duration 5,1 to 10 years	17.55	10.01 – 25.10	I^2= 98% p<0.01
Duration over 10 years	*	*	*
Cognition			
General	30.32	25.83 – 34.81	I^2= 94% p<0.01
Duration up to 5 years	24.90	22.19 – 27.62	I^2= 74% p=0.05
Duration 5,1 to 10 years	31.38	26.24 – 36.51	I^2= 95% p<0.01
Duration over 10 years	*	*	*
Communication			
General	25.36	18.90 – 31.81	I^2= 97% p<0.01
Duration up to 5 years	18.51	15.50 – 21.53	I^2= 0% p=0.44
Duration 5,1 to 10 years	26.84	19.36 – 34.32	I^2= 97% p<0.01
Duration over 10 years	*	*	*
Body discomfort			
General	34.12	29.38 – 38.86	I^2= 94% p<0.01
Duration up to 5 years	28.89	19.72 – 38.05	I^2= 89% p<0.01
Duration 5,1 to 10 years	35.10	29.81 – 40.39	I^2= 94% p<0.01
Duration over 10 years	*	*	*
PDQ-39T			
Geral	27.75	24.51 – 31.00	I^2= 93% p<0.01
Duration up to 5 years	*	*	*
Duration 5,1 to 10 years	27.75	24.51 – 31.00	I^2= 93% p<0.01
Duration over 10 years	*	*	*
*There were not studies that evaluated this factor in this condition; ** only 1 study: there was no heterogeneity test			

Discussion

Quality of life in elderly patients and with more comorbidities tend to decrease, seniors over the age of 80 years old get worse in all aspects of quality life [30]. As the severity of Parkinson's Disease is progressive and chronic it is related to poor quality of life [31]. In this meta-analysis it was possible to observe that with longer time since diagnosis of Parkinson's Disease the magnitude of quality of life measured using the PDQ-39 scale resulted in higher score, which indicates a worsening of the parameter. In another systematic review, the results are in agreement with this finding [32].

When the PDQ-39 scale was separated into different domains, it was possible to note that in all of them the Parkinson's Disease duration was the one that most influenced quality of life. According to Den Oudsten, 2007 [32], younger patients are more affected by stigma, social support and cognition when compared to older individuals. The same review showed that disease duration has a strong association with psychological factors, and the same result was found in other studies [33,34]. However, another study reported that the participation and the activity domains were the most affected [35].

The PDQ-39 scale was the most used instrument to evaluate quality of life, and was also reported in other reviews [35]. This scale covers specific Parkinson's Disease quality of life conditions, and also evaluates different situations of clinical outcomes [31].

The UPDRS scale is an instrument to evaluate the progression of the disease and to test the efficiency of a treatment. Symptoms and activities of daily living are assessed by clinical observation and self-report. This scale is subdivided in three parts, the UPDRS I indicates mental/behavior/emotional status. UPDRS II assesses activities of daily living, UDRS III evaluates motor aspects, while UPDRS IV reports complication of therapy. This meta-

analysis shows that duration increased the score in all domains, which shows high deterioration. It also showed that motor complications were the most expressive. So, changes in the motor domain were the most expressive with the disease progression [36].

This article demonstrates that the Mini Mental cognitive test score tends to reduce with the tremor duration. When periods up to 5 years and over 10 years of tremor duration were considered, the average score varied to over 7 points.

However, it is import to consider that the Mini Mental performance is directly influenced by age and education level, [37], regardless of the presence of tremor as an associated comorbidity. Prior studies on the applicability of the Mini Mental Test reported that the degree of decline in this ability was higher at older ages [38,39]. Despite this, all articles that evaluated this parameter reported low score in all cut-off periods, which does not exclude the influence of Parkinson's Disease or essential tremor in this domain.

Therefore, the biggest challenge is to evaluate the degree of influence of tremor duration in a lower cognitive test score, considering that older age is also associated with this independent variable.

In this meta-analysis, the quality of the studies was variable, there were articles with low and also high risk of bias. Another review showed that the quality of 61 articles was moderate [32].

Quality of life is influenced by many aspects such as the disease duration, neuropsychiatric disease, severity, and familiar support. In this review, we demonstrate that the decrease in of quality of life is correlated with the presence of depression, especially in the psychological domain, but it also affects mobility, activities of daily living, social stigma, and communication in a significative way. Other systematic reviews concluded that depression is the main factor that has a negative impact on the quality of life of people living with Parkinson' s Disease [40,32]. Depression has a negative and poor correlation with the discomfort domain, which is explained by the fact that depressed people tend to present a lower threshold for pain or discomfort [41].

Time was associated with quality of life, and its correlation with stigma was negative. Other systematic reviews for age did not show a strong correlation with quality of life [42]. We could observe a stronger correlation between time and cognition. Time also impacted other quality of life scales, QUEST, specific for essential tremor and DASS. A more intense correlation between time and cognition was observed. Severity was measured using the Hoen & Yarh scale and showed great impact on mobility, activity of daily living, and the communication domain. The Hoen & Yarh scale presented a negative correlation with the social domain. Another systematic review reported that severity impacted those individuals' quality of life [43].

The contribution of the medications used to treat essential tremor is the improvement in quality of life. The Levodopa and Dopamine agonists modify the evolution of the tremor. Although the impact of the therapy with pills is out of the scope of this research, some articles described the use of this therapeutic option, so a specific analysis of the magnitude of the pharmacological intervention in quality of life should be consider in the future.

One of the limitations of this study is that the number of studies that analyze other conditions, different from Parkinson's disease, is low. This fact reduces the possibility to expand the results to include other pathologies that involve tremor such as essential tremor. Another aspect is that the use of different scales to assess quality of life makes it hard to compare these studies. In addition, different scales to assess depression and severity in Parkinson's Disease and Essential Tremor were also used.

The main challenge in this meta-analysis was the absence of some time periods and the low heterogeneity in some domains and times. This deficiency shows the importance of follow-up in patients with Parkinson's Disease, since the diagnosis and throughout its development to conclude which quality of life domains are the most affected and to enable specific intervention to improve it.

Soh, 2016 [43], showed in a systematic review that specific measurements of quality of life domains did not consider time since diagnosis and the patients' sociodemographic factors. However, both variables might present a strong correlation.

The question regarding the possible delay in the diagnosis of Parkinson's Disease or Essential Tremor remains open. In this situation patients could already have presented the symptoms evaluated for a longer period than that considered by the studies. It can be explained by a delay in the search for a doctor, or a delay in the disease screening. None of the articles considered this issue. Therefore, further studies should be developed including this aspect.

In conclusion, the progression of Parkinson disease and essential tremor impact significantly in the health-related quality of life and in other aspects of the disease. Further studies should be conducted to explain if the time to diagnosis by a doctor impact on the life quality.

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