Journal of Neurology (2019) 266:3119–3125
https://doi.org/10.1007/s00415-019-09545-0

ORIGINAL COMMUNICATION

Considerations before initiating therapy in Parkinsonism: basing on the quality of life

Shu-Jin He[1] · Zhen-Yang Liu[1,2] · Yu-Jie Yang[1] · Cong Shen[1] · Yu-Jie Du[1] · Xin-Yue Zhou[1] · Jue Zhao[1] · Yi-Min Sun[1] · Ke Yang[1] · Jian-Jun Wu[1] · Feng-Tao Liu[1] · Jian Wang[1]

Received: 29 June 2019 / Revised: 11 September 2019 / Accepted: 13 September 2019 / Published online: 18 September 2019

Abstract

Objective Improvement of quality-of-life (QoL) has been termed as a primary objective in initiating therapy in both Parkinson's disease (PD) and multiple system atrophy Parkinsonian subtype (MSA-P). We aimed to compare the determinants of life quality in drug naïve PD and MSA-P patients.

Methods Eighty-six drug-naïve PD patients and thirty-five drug-naïve MSA-P patients were included to explore the determinants of QoL. Demographic information, motor deficits, and non-motor symptoms were included in the clinical assessment.

Results Both motor and non-motor functions were more severely impaired in the drug-naïve MSA-P patients, with higher PDQ-39 scores indicating poorer QoL. Physical discomfort and stigma were the main affected sub-domains in PD, while mobility and activity of daily life were the main affected ones in MSA-P. BECK depressive scores and UPDRS-III scores were independent variables of PDQ-39 in MSA-P patients. Age, depression, disease stages and non-motor scores were independent variables of PDQ-39 in PD patients.

Interpretation Drug-naïve MSA-P patients suffered from more severe motor and non-motor disability, as well as poorer QoL. Depression and non-motor symptoms were proved to be the most critical determinants for QoL in PD, while motor function was supposed to be the major determinant for MSA-P. When initiating therapy, physicians need to focus more on motor functions in drug-naïve MSA-P patients, but on depression in PD patients.

Keywords Quality of life · Parkinson's disease · Multiple system atrophy · Drug-naïve

Introduction

It has been widely discussed when and how to initiate the medical treatment in Parkinson's disease (PD) and related neurodegenerative disorders, either start immediately on diagnosis or wait until the functional disability occurs [7, 10]. The quality of life (QoL), one of the major primary outcomes, has been adopted in a number of double-blind randomized clinical trials, and it is believed that the improvement of QoLis one of the primary objectives to initiate medical treatment [12, 21]. Therefore, it is of great necessity to clarify the QoL status in untreated PD and related disorders for initiating precision therapy for final QoL improvement [11].

To initiate the medication in PD, the motor symptoms, which are the core manifestations and response quite well to dopaminergic therapy, are currently the first consideration. The Parkinsonian subtype of multiple system atrophy (MSA-P) often mimics Parkinson's disease (PD) in motor symptoms including tremor, bradykinesia, rigidity and postural instability [4, 38, 40]. Therefore, dopaminergic therapy focusing on the shared motor symptoms is empirically initiated in MSA-P [20], which was similar to PD. However, MSA-P patients respond poorly to levodopa, suffer severe autonomic failures and degenerate much faster than PD patients [31]. Furthermore, QoL is not only influenced

Shu-Jin He, Zhen-Yang Liu and Yu-Jie Yang contributed equally to the manuscript.

✉ Feng-Tao Liu
liufengtao@fudan.edu.cn

✉ Jian Wang
wangjian_hs@fudan.edu.cn; wangjian336@hotmail.com

[1] Department of Neurology and National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, 12 Wulumuqi Zhong Road, Jing'an District, Shanghai 200040, China

[2] Intensive Care Unit, Huashan Hospital (West Campus), Fudan University, Shanghai 201107, China

by motor symptoms, but also by non-motor manifestations. Therefore, to make more precise and individualized treatment strategy to improve the QoL, physicians need to explore in detail the characteristics and differences in QoL of PD and MSA-P, especially in drug-naïve condition.

Herein, we recruited a cohort of drug-naïve PD and MSA-P patients to investigate the determinants of their QoL. By focusing on the detected determinants, our study might offer precise suggestions to initiate the medical therapy in MSA-P and PD with better anticipations of final QoL improvements.

Patients and methods

Patients

Drug-naïve PD patients and drug-naïve MSA-P patients were consecutively recruited from January 2011 to January 2016 in Huashan Hospital, Fudan University. All PD patients were diagnosed according to the criteria of the United Kingdom PD Society Brain Bank [15, 25] by at least two specialists on movement disorders, and confirmed by at least 2-year follow-up. All MSA-P patients were diagnosed according to the probable MSA clinical diagnostic criteria [13] and identified as the Parkinsonian subtype (MSA-P) according to the predominant motor symptom. All participants signed informed consent in accordance with the Declaration of Helsinki before participation. The study was approved by the Human Studies Institutional Review Board, Huashan Hospital, Fudan University.

Clinical assessments

Every patient received a full set of clinical assessment comprising of demographic information, motor function, non-motor disability and health-related life quality. Demographic information, including gender, age, age of onset and disease duration, was collected over interview and questionnaire. Clinical examinations were carried out by at least two movement disorder specialists at Huashan Hospital. The motor function was measured by Hoehn and Yahr stage (H&Y) and Unified Parkinson's Disease Rating Scale—part III (UPDRS-III). Non-motor symptom was assessed by the Non-Motor Symptom Questionnaire (NMSQ) [5], which is composed of 30 items classified into 9 sub-domains. Other non-motor symptoms including Rapid-eye-movement (REM)-sleep behavior disorder (RBD) and daytime somnolence were assessed by specific questionnaire such as REM-sleep Behavior Disorder Screening Questionnaire (RBDSQ) [36] and Epworth Sleepiness Scale (ESS) [6]. The patient's depression was assessed by Beck Depression Inventory (BDI) [24, 32], as well as Geriatric Depression Scale (GDS) [9].

The QoL in our study was assessed using Parkinson's Disease Quality of Life Questionnaire (PDQ-39) [34]. PDQ-39 is a most widely used PD-related self-reported questionnaire, which comprised 39 items covering eight domains: mobility, activity of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort [34]. All of the items are scored on a 5-point ordinal scale ranging from 0 ("never") to 4 ("always"). Original PDQ-39 scores were standardized to summary index (PDQ-39 SI), dividing the raw scores by the maximum possible raw score, and multiplying by 100 (range from 0 to 100). Higher scores indicate worse QoL. All the rating scales were validated in Chinese version.

Statistical analysis

Statistical analysis was performed using SPSS software (Version 17.0; SPSS, lnc. Chicago, IL). Continuous data were examined of normality using Kolmogorov–Smirnov's test. Student's *t* test was used for the analysis of the continuous data which was normally distributed and Mann–Whitney's *U* test was used for the data which were not. Pearson's Chi-squared was adopted for the analysis of categorical variables. Correlations between QoL and baseline clinical parameters were assessed using Spearman's rho correlation coefficient. We evaluated the impact of clinical features by linear regression model, and multiple stepwise regression was used to uncover the main determinants of the life quality in PD and MSA-P patients respectively. The significance level was set at 0.05.

Results

Demographics and clinical characteristics

In our study, 86 de novo PD patients (43 men, 43 women, 59.05 ± 10.50 years old) and 35 de novo MSA-P patients (19 men, 16 women, 57.63 ± 7.72 years old) were finally recruited. Demographic information and clinical characteristics were presented in Table 1. No difference was reported between the two groups in demographic information.

Motor and non-motor characteristics

Both H&Y ratings and UPDRS motor scores were significantly higher in MSA-P patients than PD patients, at the first diagnosis. A higher incidence of rigidity was found in MSA-P patients, but PD patients had higher incidence of tremor than MSA-P patients (Table 1).

Table 1 Demographics and clinical dysfunctions in PD and MSA-P patients

	PD, $N=86$	MSA-P, $N=35$	p value
Men/women	43/43	19/16	0.669
Age (mean ± SD)	59.05 ± 10.50	57.63 ± 7.72	0.242
Age of onset (mean ± SD)	56.49 ± 11.52	55.89 ± 7.24	0.455
Disease duration (months) (quartiles)	17(5, 34)	21(7, 29)	0.812
H&Y stage [median (quartiles)]	2.00 (1.00, 2.00)	3.00 (2.00, 4.00)	< 0.001
UPDRS-III Score	25.43 ± 10.98	40.67 ± 13.69	< 0.001
Tremor	76/86 (88%)	15/35 (43%)	< 0.001
Rigidity	46/86 (53%)	26/35 (74%)	0.035
Bradykinesia	77/86 (90%)	34/35 (97%)	0.168
NMSQ	7.72 ± 4.59	13.38 ± 5.65	< 0.001
Digestive	1.45 ± 1.36	3.12 ± 1.32	< 0.001
Urinary	0.92 ± 0.75	1.53 ± 0.71	< 0.001
Memory	1.01 ± 1.02	1.03 ± 1.00	0.857
Hallucination/delusions	0.20 ± 0.40	0.35 ± 0.54	0.126
Depression/anxiety	0.70 ± 0.83	1.00 ± 0.89	0.084
Sexual	0.58 ± 0.83	1.03 ± 0.87	0.007
Cardiovascular	0.36 ± 0.57	1.15 ± 0.82	< 0.001
Sleep disorder	1.49 ± 1.33	2.56 ± 1.65	0.001
Miscellany	1.05 ± 1.04	1.62 ± 1.46	0.063
RBDSQ	3.19 ± 2.53	4.57 ± 3.51	0.052
ESS	4.54 ± 4.21	5.43 ± 5.61	0.705
GDS	8.58 ± 5.75	14.29 ± 8.29	< 0.000
BDI	9.94 ± 7.73	17.00 ± 11.91	0.002

PD Parkinson's disease, *MSA-P* multiple system atrophy-Parkinsonian subtype, *H&Y stage* Hoehn and Yahr stage, *UPDRS-III* Unified Parkinson's Disease Rating Scale part III, *NMSQ* Non Motor Symptoms Questionnaire, *RBDSQ* Rapid-Eye-Movement Sleep Behavior Disorder Screening Questionnaire, *ESS* Epworth Sleepiness Score, *GDS* Geriatric Depression Scale, *BDI* Beck s

In general, non-motor dysfunctions detected by NMSQ were more severe in MSA-P patients (13.38 ± 5.65 vs. 7.72 ± 4.59, $p < 0.001$) in most sub-domains (Table 1). In sleep disorders, MSA-P patients might experience more severe RBD symptoms, with a trend of higher RBDSQ scores, though not reaching statistically significance level ($p = 0.052$). However, they might have similar daytime sleepiness problems as PD patients, with similar ESS scores. In terms of depression, both BDI scores and GDS scores were significantly higher in MSA-P comparing with PD.

Quality of life assessment and reassessment after 2-year follow up

In our population at the first diagnosis, MSA-P patients had worse life quality compared with PD patients (38.43 ± 18.37 vs. 13.73 ± 10.27, $p < 0.001$) according to the PDQ-39 SI score (Table 2). Further analysis indicated that the most affected sub-domains in de novo MSA-P were mobility (60.64 ± 27.00) and activity of daily living (48.81 ± 33.93), while physical discomfort (21.71 ± 20.38), cognitive impairment (17.59 ± 15.05) and emotional well-being (16.86 ± 16.65) in de novo PD patients.

Table 2 Quality of life assessment in drug-naïve PD and MSA-P patients

	PD, $N=86$	MSA-P, $N=35$	p value
PDQ-39 SI	13.73 ± 10.27	38.43 ± 18.37	< 0.001
Mobility SI	13.28 ± 17.13	60.64 ± 27.00	< 0.001
Activity of daily living SI	11.24 ± 14.08	48.81 ± 33.93	< 0.001
Emotional well-being SI	16.86 ± 16.65	29.17 ± 26.16	0.024
Stigma SI	16.79 ± 21.57	28.93 ± 27.41	0.012
Social support SI	3.78 ± 9.10	7.38 ± 12.59	0.088
Cognitive impairment SI	17.59 ± 15.05	27.32 ± 20.51	0.013
Communication SI	6.59 ± 11.37	31.19 ± 24.78	< 0.001
Physical discomfort SI	21.71 ± 20.38	27.86 ± 25.08	0.269

PD Parkinson's disease, *MSA-P* multiple system atrophy-Parkinsonian subtype, *PDQ-39* 39-item Parkinson's disease questionnaire, *SI* summary index

Determinants of life quality

In de novo PD patients, the ratings in motor functions [H&Y stages ($r = 0.33$, $p = 0.002$), UPDRS-III scores ($r = 0.31$, $p = 0.004$)], non-motor functions [NMSQ

($r = 0.48$, $p < 0.001$), as well as the NMS subdomains of digestive ($r = 0.29$, $p = 0.007$), memory ($r = 0.36$, $p < 0.001$), depression/anxiety ($r = 0.55$, $p < 0.001$) and miscellany ($r = 0.34$, $p = 0.002$)], somnolence (ESS, $r = 0.40$, $p < 0.001$) and emotional well-beings [BDI ($r = 0.52$, $p < 0.001$), GDS ($r = 0.59$, $p < 0.001$)] correlated significantly with PDQ-39 SI. In MSA-P patients, the variables correlated greatly with PDQ-39SI include H&Y stages ($r = 0.51$, $p = 0.004$), UPDRS-III scores ($r = 0.72$, $p < 0.001$), BDI ($r = 0.63$, $p < 0.001$), GDS ($r = 0.58$, $p < 0.001$), NMSQ ($r = 0.52$, $p = 0.002$), and NMS subdomains of digestive ($r = 0.43$, $p = 0.010$), depression ($r = 0.42$, $p = 0.013$) and miscellany ($r = 0.50$, $p = 0.003$).

To explore the determinants of life quality in drug-naïve PD and MSA-P patients, we conducted the linear regression model based on the results of correlation analysis. For drug-naïve PD patients, depression was the most important determinant of life quality ($\beta = 0.468$, $p < 0.001$), followed by UPDRS-III ($\beta = 0.230$, $p = 0.011$) and NMSQ ($\beta = 0.199$, $p = 0.042$). For MSA-P patients, however, UPDRS-III motor score showed the strongest impact on PDQ-39 SI ($\beta = 0.502$, $p = 0.008$) (Table 3).

Furthermore, in a multiple stepwise analysis with all variables correlated with PDQ-39 SI entered, GDS, NMSQ, H&Y ratings and age were the determinants of PDQ-39 SI in PD patients; BDI score and UPDRS motor score were the determinants of PDQ-39 SI in MSA-P patients (Table 4).

Table 3 Impact of motor, non-motor symptoms on the PDQ-39SI based on the linear regression model in drug-naïve PD and MSA-P patients

	Standardized β	p value
PD, $R^2 = 0.718$		
Age	−0.158	0.068
Disease duration	0.085	0.316
Gender	−0.015	0.862
GDS	0.468	< 0.001
UPDRS-III	0.230	0.011
NMSQ	0.199	0.042
MSA-P, $R^2 = 0.779$		
Age	−0.057	0.752
Disease duration	0.206	0.284
Gender	−0.128	0.411
GDS	0.284	0.150
UPDRS-III	0.502	0.008
NMSQ	0.124	0.557

PD Parkinson's disease, *GDS* Geriatric Depression Scale, *UPDRS-III* Unified Parkinson's Disease Rating Scale part III, *NMSQ* Non-Motor Symptoms Questionnaire, *MSA-P* multiple system atrophy-Parkinsonian subtype

Table 4 Determinants of PDQ-39SI depending on the multiple stepwise analysis in MSA-P and PD patients

	Standardized β	p value
PD, $R^2 = 0.507$		
GDS	0.431	< 0.001
H&Y stage	0.290	0.001
Age	−0.192	0.020
NMSQ	0.218	0.035
MSA-P, $R^2 = 0.613$		
BDI	0.369	0.026
UPDRS-III	0.569	0.001

PD Parkinson's disease, *GDS* Geriatric Depression Scale, *H&Y stage* Hoehn and Yahr stage, *NMSQ* Non-Motor Symptoms Questionnaire, *MSA-P* multiple system atrophy-Parkinsonian subtype, *BDI* Beck Depression Inventory, *UPDRS-III* Unified Parkinson's Disease Rating Scale part III

Discussion

In this study, we investigated the clinical characteristics and compared the determinants of the QoL in drug-naïve PD and MSA-P patients. Non-motor symptoms, especially depression, played a crucial part in the life quality of PD patients. Compared with PD, the MSA-P patients suffered from worse QoL, where motor function was the most severely injured domain. Our findings may contribute to initiate more precise therapeutic strategies in drug-naïve PD and MSA-P to finally improve QoL.

Although it can be challenging to distinguish MSA-P from PD in the early stage due to the overlapping Parkinsonism [17], our study demonstrated that some clinical manifestations might be helpful. In the MDS clinical diagnostic criteria for PD, the early severe autonomic failure in the first 5 years was termed as the red flag for the diagnosis of PD [22]. Compared with PD, the MSA-P patients presented more severe motor and non-motor dysfunctions. Meanwhile, 42% of the MSA-P patients reported tremor, but the percentage in PD was 88%. According to the existing studies, less than 10% of MSA patients present with typical Parkinsonian "pill-rolling" rest tremor, suggesting that tremor might be an important point for the differentiation between MSA-P and PD.

In the current study, physical discomfort and cognitive impairment scored higher than motor dysfunction in drug-naïve PD patients, indicating the non-motor factors probably making great influence on the quality of life. Similarly, Gordon W. Duncan reported that the physical discomfort scored highest, with mobility and activity of daily living being the second in early PD (disease duration 6.36 ± 5.9 months) [8]. However, that study might have been cofounded by medication therapy [8]. In our study, the multiple forward stepwise analysis identified GDS, NMSQ, age and H&Y as

independent factors on PDQ-39 for PD patients, with GDS being the strongest determinant of QoL, emphasizing the effects of depression. Similar results have been published by several studies, claiming that depression was the greatest contributor to the decline of QoL in PD patients [16, 26]. Therefore, physicians should pay more attention on the depression in drug-naïve PD patients to maximize the benefits on QoL. In a recent published update on the treatment of non-motor symptoms of PD [28], the treatment on depression has been systemically suggested. However, the treatment efficacy of depression in clinical practice is far from satisfaction [2], where less than 20% of depressed PD patients undertook the anti-depressive treatment [37]. It is not only because the importance of depression was underestimated by physicians [35], but also the depressive symptom in early PD is frequently ignored [29]. Reliable detecting tools of depression are highly recommended in the clinical practice in order to improve the diagnosis rates, such as the self-rating questionnaires.

Although GDS and BDI were the most popular self-report measurements of depression, there is a preference to practical application depending on the target population. It is notable that the GDS is supposed to have higher sensitivity and specificity in PD patients, compared with BDI [14], while BDI is more widely used among MSA-P patients [3]. Not coincidentally, the multiple stepwise analysis in our study has exactly chosen GDS as one independent factors of PDQ-39 for PD and BDI for MSA-P, supporting the preference of depression scale selection in PD and MSA-P. However, further exploration will be needed to confirm this idea.

The MSA-P patients experienced of much more severe non-motor symptoms than PD patients, which was probably due to the autonomic failures [18, 19]. However, different from the result that non-motor symptoms played the strongest role in QoL of drug-naïve PD patients, motor dysfunctions showed the strongest effects on the QoL of drug-naïve MSA-P in our study. In the drug-naïve stage, both H&Y ratings and UPDRS-III scores were significant higher in MSA-P patients than PD, consisting with former results in patients with much longer disease duration [33]. Meanwhile, mobility and ADL were the most affected subdomains with absolutely higher scores in PDQ-39, and the UPDRS-III scores were the independent and strongest factors of QoL in stepwise multiple analysis, emphasizing the strongest effects of motor deficits on life quality of MSA-P. In advanced MSA-P patients, Schrag reported motor-related sub-domains still being the most severely injured domain in QoL of MSA-P [27]. In a study with PD and MSA-P patients that matched for motor disability on UPDRS-III score, no difference was reported in QoL [30], supporting motor dysfunction as a major reason of poorer QoL in MSA-P comparing with PD. Taken together, it was indicated that motor function plays the most important role in QoL of MSA-P.

In clinical practice, physicians were sometimes misled by the impression that the MSA-P patients response poor to dopaminergic therapy. Actually, up to 30–40% MSA patients once reported of positive, but not excellent response to dopaminergic treatment [1, 33, 39], although the medical response usually declined after few years [23]. Such a beneficial levodopa response was also reported in a critique of the second criteria for multiple system atrophy [30]. Considering the central role of motor dysfunction in the QoL of MSA-P patients, unreserved dopaminergic treatment with extra attention on the motor dysfunction was highly recommended in initiating the medical therapy on those untreated patients.

Strength and limitation

As we know, this study is the first attempt to compare the determinants of QoL in PD and MSA-P patients without the confounders of medication, which will offer more evidence for making strategies on the initiation of medical therapy. Based on the results, we found significant difference in the determinants of QoL and suggested an initial treatment strategy with emphasis on depression status in PD patients and motor dysfunction in MSA-P patients. Meanwhile, we should admit that there are some limitations in our work. Firstly, the PDQ-39 questionnaire is not the most proper measure of QoL for MSA patients, after all, many specialized features such as cerebellar symptoms cannot be reflected in it. Fortunately, the PDQ-39 showed acceptable reliability and construct validity when tested in MSA population [27], and the cerebellar symptoms are not that obvious in the early stage of our MSA-P patients. Secondly, although UPDRS-III was also proved to be an accurate measure of Parkinsonism severity in MSA [33], we should admit that it might be contaminated by the cerebellar and pyramidal symptoms of MSA [33]. Therefore, we included only the PD patients and MSA-P patients in the drug-naïve status in this study, trying to eliminate the confounders as much as possible. In the current study, we did not make the diagnosis of depression by neuropsychologists at the time of diagnosis, which limited the further exploration on the detailed effects of depression.

Conclusions

In our study, depression and non-motor symptoms were proved to be the most critical factor of the PDQ-39 in PD, while motor function was supposed to be the major determinant for QoL in MSA-P according to our study. To achieve the best therapeutic efficacy to improve QoL, physicians need to focus more on depression in PD patients and motor

dysfunction in drug-naïve MSA-P patients when initiating the medical therapy.

Acknowledgements Jian Wang received the research funding from Ministry of Science and Technology of China (Grant No: 2016YFC1306500, 2016YFC1306504) and the National Nature Science Foundation of China (Grant No: 81771372, 81571232). Feng-Tao Liu received the grand of the National Nature Science Foundation of China (Grant No: 81701250) and Shanghai Municipal Commission of Science and Technology (Grant No: 17JC1401400). Yu-Jie Yang has received financial support from China Postdoctoral Science Foundation (Grant No: 2017M610227, 2018T110350).

Author contributions All authors' roles in the project and preparation of the manuscript are listed as follows. (1) Research project: A. Conception by JW, YJY, JJW and FTL; B. Organization by ZYL, SJH, CS, YJD and YMS; C. Execution by SJH, YJY, XYZ, ZYL and FTL. (2) Statistical Analysis: A. Design by JW and FTL; B. Execution by SJH, ZYL, CS, YJD and JZ; C. Review and Critique by JW, YMS and FTL. (3) Manuscript: A. Writing of the first draft by SJH, YJY, XYZ, ZYL and FTL; B. Review and Critique by JW, and FTL.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard This study was approved by the Human Studies Institutional Review Board, Huashan Hospital, Fudan University.

References

1. Albanese A, Colosimo C, Bentivoglio AR, Fenici R, Melillo G, Colosimo C, Tonali P (1995) Multiple system atrophy presenting as parkinsonism: clinical features and diagnostic criteria. J Neurol Neurosurg Psychiatry 59:144–151
2. Bega D, Wu SS, Pei Q, Schmidt PN, Simuni T (2014) Recognition and treatment of depressive symptoms in Parkinson's disease: the NPF dataset. J Parkinson Dis 4:639–643
3. Benrud-Larson LM, Sandroni P, Schrag A, Low PA (2005) Depressive symptoms and life satisfaction in patients with multiple system atrophy. Mov Disord 20:951–957
4. Bu LL, Liu FT, Jiang CF, Guo SS, Yu H, Zuo CT, Wu P, Wang J (2018) Patterns of dopamine transporter imaging in subtypes of multiple system atrophy. Acta Neurol Scand 138:170–176
5. Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, Brown RG, Koller W, Barone P, MacPhee G, Kelly L, Rabey M, MacMahon D, Thomas S, Ondo W, Rye D, Forbes A, Tluk S, Dhawan V, Bowron A, Williams AJ, Olanow CW (2006) International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord 21:916–923
6. Chen NH, Johns MW, Li HY, Chu CC, Liang SC, Shu YH, Chuang ML, Wang PC (2002) Validation of a Chinese version of the Epworth sleepiness scale. Qual Life Res 11:817–821
7. Clarke CE, Patel S, Ives N, Rick C, Wheatley K, Gray R (2011) Should treatment for Parkinson's disease start immediately on diagnosis or delayed until functional disability develops? Mov Disord 26:1187–1193
8. Duncan GW, Khoo TK, Yarnall AJ, O'Brien JT, Coleman SY, Brooks DJ, Barker RA, Burn DJ (2014) Health-related quality of life in early Parkinson's disease: the impact of nonmotor symptoms. Mov Disord 29:195–202
9. Ertan FS, Ertan T, Kiziltan G, Uygucgil H (2005) Reliability and validity of the Geriatric Depression Scale in depression in Parkinson's disease. J Neurol Neurosurg Psychiatry 76:1445–1447
10. Espay AJ, Lang AE (2017) Common myths in the use of levodopa in Parkinson disease: when clinical trials misinform clinical practice. JAMA Neurol 74:633–634
11. Fereshtehnejad SM (2016) Strategies to maintain quality of life among people with Parkinson's disease: what works? Neurodegener Dis Manag 6:399–415
12. Floden D, Cooper SE, Griffith SD, Machado AG (2014) Predicting quality of life outcomes after subthalamic nucleus deep brain stimulation. Neurology 83:1627–1633
13. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Durr A, Fowler CJ, Kaufmann H, Klockgether T, Lees A, Poewe W, Quinn N, Revesz T, Robertson D, Sandroni P, Seppi K, Vidailhet M (2008) Second consensus statement on the diagnosis of multiple system atrophy. Neurology 71:670–676
14. Goodarzi Z, Mrklas KJ, Roberts DJ, Jette N, Pringsheim T, Holroyd-Leduc J (2016) Detecting depression in Parkinson disease: a systematic review and meta-analysis. Neurology 87:426–437
15. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181–184
16. 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 Out 13:83
17. Kim HJ, Stamelou M, Jeon B (2016) Multiple system atrophy-mimicking conditions: diagnostic challenges. Parkinsonism Relat Disord 22(Suppl 1):S12–15
18. Kim JB, Kim BJ, Koh SB, Park KW (2014) Autonomic dysfunction according to disease progression in Parkinson's disease. Parkinsonism Relat Disord 20:303–307
19. Kim JS, Lee SH, Oh YS, Park JW, An JY, Park SK, Han SR, Lee KS (2016) Cardiovascular autonomic dysfunction in mild and advanced Parkinson's disease. J Mov Disord 9:97–103
20. Krismer F, Wenning GK (2017) Multiple system atrophy: insights into a rare and debilitating movement disorder. Nat Rev Neurol 13:232–243
21. Pahwa R, Lyons KE (2014) Treatment of early Parkinson's disease. Curr Opin Neurol 27:442–449
22. 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
23. Quinn N, Wenning G (1994) Multiple system atrophy. Br J Hosp Med 51:492–494
24. Richter P, Werner J, Heerlein A, Kraus A, Sauer H (1998) On the validity of the Beck Depression Inventory: a review. Psychopathology 31:160–168
25. Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G (2016) Accuracy of clinical diagnosis of Parkinson disease: a systematic review and meta-analysis. Neurology 86:566–576
26. Schrag A, Jahanshahi M, Quinn N (2000) What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 69:308–312
27. Schrag A, Jenkinson C, Selai C, Mathias C, Quinn N (2007) Testing the validity of the PDQ-39 in patients with MSA. Parkinsonism Relat Disord 13:152–156
28. Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D, Sampaio C, and sthe collaborators of

the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine C (2019) Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. Mov Disord 34:180–198
29. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ (2002) Non-recognition of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 8:193–197
30. Stankovic I, Quinn N, Vignatelli L, Antonini A, Berg D, Coon E, Cortelli P, Fanciulli A, Ferreira JJ, Freeman R, Halliday G, Hoglinger GU, Iodice V, Kaufmann H, Klockgether T, Kostic V, Krismer F, Lang A, Levin J, Low P, Mathias C, Meissner WG, Kaufmann LN, Palma JA, Panicker JN, Pellecchia MT, Sakakibara R, Schmahmann J, Scholz SW, Singer W, Stamelou M, Tolosa E, Tsuji S, Seppi K, Poewe W, Wenning GK, Movement Disorder Society Multiple System Atrophy Study G (2019) A critique of the second consensus criteria for multiple system atrophy. Mov Disord 34:975–984
31. Stefanova N, Bucke P, Duerr S, Wenning GK (2009) Multiple system atrophy: an update. The Lancet Neurol 8:1172–1178
32. Sun XY, Li YX, Yu CQ, Li LM (2017) Reliability and validity of depression scales of Chinese version: a systematic review. Zhonghua Liu Xing Bing Xue Za Zhi 38:110–116
33. Tison F, Yekhlef F, Chrysostome V, Balestre E, Quinn NP, Poewe W, Wenning GK (2002) Parkinsonism in multiple system atrophy: natural history, severity (UPDRS-III), and disability assessment compared with Parkinson's disease. Mov Disord 17:701–709
34. Tsang KL, Chi I, Ho SL, Lou VW, Lee TM, Chu LW (2002) Translation and validation of the standard Chinese version of PDQ-39: a quality-of-life measure for patients with Parkinson's disease. Mov Disord 17:1036–1040
35. Uitti RJ (2012) Treatment of Parkinson's disease: focus on quality of life issues. Parkinsonism Relat Disord 18(Suppl 1):S34–36
36. Wang Y, Wang ZW, Yang YC, Wu HJ, Zhao HY, Zhao ZX (2015) Validation of the rapid eye movement sleep behavior disorder screening questionnaire in China. J Clin Neurosci 22:1420–1424
37. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB (2003) Recognition and treatment of depression in Parkinson's disease. J Geriatr Psychiatry Neurol 16:178–183
38. Wenning GK, Ben-Shlomo Y, Magalhaes M, Daniel SE, Quinn NP (1994) Clinical features and natural history of multiple system atrophy: an analysis of 100 cases. Brain 117(Pt 4):835–845
39. Wenning GK, Ben-Shlomo Y, Magalhaes M, Daniel SE, Quinn NP (1995) Clinicopathological study of 35 cases of multiple system atrophy. J Neurol Neurosurg Psychiatry 58:160–166
40. Wenning GK, Tison F, Ben Shlomo Y, Daniel SE, Quinn NP (1997) Multiple system atrophy: a review of 203 pathologically proven cases. Mov Disord 12:133–147