RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2024, Volume 58, no. 4, pages: 422–428
DOI: 10.5603/pjnns.99624

ISSN: 0028-3843, e-ISSN: 1897-4260

Are 5-2-1 Delphi criteria and MANAGE-PD useful screening tools for general neurologists for qualification to device-aided therapies in advanced Parkinson's Disease?

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ABSTRACT

Aim of study. We sought to compare MANAGE-PD and 5-2-1 Delphi criteria which are two commonly used and approved screening tools in Parkinson's Disease, in order to highlight their strengths and limitations.

Clinical rationale for study. Timely intervention with device-aided therapies is vital as it enables improving motor symptoms, lowering the dosage and side-effects of dopaminergic treatment, and improving patients' and caregivers' quality of life. Various screening tools have been created to help clinicians find the best candidates for device-aided therapies (DAT) for advanced Parkinson's Disease. In this study, we aimed to compare the 5-2-1 Delphi criteria to MANAGE-PD to determine how they could be used specifically to maximise their potential.

Material and methods. All of the patients (260) included in this study were DAT-naive, > 18 years of age, diagnosed with Parkinson's Disease, and had been referred to the Department of Neurology for qualification for advanced therapies over a 4-year period (2019-2022). They were subjected to both 5-2-1 Delphi criteria and MANAGE-PD tools and divided into sub-groups based on the results of the screening. The data of patients was then statistically analysed.

Results. In the study group, 51 patients (19.5%) met all three of the 5-2-1 criteria, and 123 (47.1%) patients were categorised as '3' in MANAGE-PD, meaning that they may benefit from DAT. Finally, at the local centre level, 64 (24.5%) patients were qualified for DAT. 22 (34.4%) patients who were qualified for DAT by a clinician did not meet the 5-2-1 criteria.

Conclusions. The 5-2-1 scheme based on the data from this study was characterised by a 92.5% specificity level and 65.1% sensitivity level compared to 69.5% specificity and 98.4% sensitivity level of MANAGE-PD.

Clinical implications. We found that MANAGE-PD has a better screening potential of DAT admission than 5-2-1 criteria. While both tools are reliable and valuable in daily practice, our study suggests that some patients may be omitted when using only less complicated tools such as 5-2-1 during the assessment.

Keywords: 5-2-1 Delphi criteria, MANAGE-PD, Parkinson's Disease, device-aided therapy

(*Neurol Neurochir Pol 2024; 58 (4): 422–428*)

Introduction

Parkinson's Disease remains one of the most frequent neurodegenerative disorders, causing significant loss of quality of life and imposing an economic burden on those affected as well as their families [1, 2]. It is an uncurable disorder with heterogenous symptoms affecting, for example, movement, cognition, behaviour, and autonomic system resulting in functional impairment [1]. Adequate and timely management of the progression and prevention of disability, especially in the advanced stages of the disease, pose a significant challenge that has led to the development of a variety of device-aided therapies.

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Received: 02.03.2024 Accepted: 11.06.2024 Early publication date: 05.07.2024

As the disease progresses, conventional oral therapy becomes insufficient due to decreased response to medication, motor fluctuations and dyskinesia, as well as non-motor side-effects of the higher doses needed. Currently available therapies after the exhaustion of conventional treatment are levodopa/carbidopa intestinal gel infusion (LCIG), deep brain stimulation (DBS) and apomorphine subcutaneous infusion (SCAI).

However, a lack of objective and standardised diagnostic criteria allowing for the identification of patients with advanced disease in clinical practice poses difficulties and hinders progress in the treatment of Parkinson's Disease (PD). Substantial efforts have been made to help clinicians recognise the pivotal moment when a patient becomes eligible for device-aided therapies (DAT). Many different methods and procedures have been tried to identify advanced PD (aPD). Attempts have been made to create various scales to help in the diagnosis, such as the Parkinson's Disease Composite Scale (PDCS), and the Cuestionario De Entermeted de Parkinson Avanzada (Questionnaire for Advanced Parkinson's Disease; CDEPA) [22]. In the Delphi study, a group of experts identified 15 clinically relevant indicators to help quantify aDP (six motor symptoms [MS], five non-motor symptoms [NMS], and four functional impairments) [5]. Ultimately, the three most crucial ones were selected, and thus the 5-2-1 criteria were created.

The 5-2-1 criteria mean '5' as in five or more doses of L-dopa per day; '2' means > 2 hours of 'OFF' time during the waking day, and '1' means the presence for at least one hour of troublesome dyskinesia. Although primarily developed to assign patients into a widely discussed 'advanced PD' (aPD) category, it is commonly used to identify patients who may benefit from DAT. 5-2-1-positive patients have been proven to bear a significantly higher clinical and socio-economic burden compared to PD patients who do not meet these criteria [3–5, 7].

Recently, Making Informed Decisions to Aid Timely Management of Parkinson's Disease (MANAGE-PD) was introduced to help general neurologists to recognise aPD patients who could benefit from DAT. MANAGE-PD, besides classic motor symptoms, includes additional symptoms associated with aPD such as dystonia with pain, hallucinations without insight, number of falls, impairment in performing ADL, freezing of gait, impulse control disorder, and unpredictable motor fluctuations. It works as a single-choice questionnaire resulting in assigning the patient to one of three categories, of which the third contains individuals who may benefit from device-aided therapies.

MANAGE-PD has been validated and proven as a valuable clinical instrument [8, 9]. The goal of our study was to determine how results of the screening done with the aforementioned tools compare to real-world clinician-based evaluation resulting in admission to DAT.

Clinical rationale for study

Timely intervention with device-aided therapies is crucial as it enables improving motor symptoms, lowering the dosage and side-effects of dopaminergic treatment, and improving patients' and caregivers' quality of life. Various screening tools have been created to help clinicians find the best candidates for device-aided therapies (DAT) for aPD. In this study, we aimed to compare the 5-2-1 Delphi criteria to MANAGE-PD in order to determine how they could be used specifically to maximise their potential.

Material and methods

All of the patients included in this study were DAT-naive, > 18 years old, diagnosed with Parkinson's Disease, and referred to the Department of Neurology for qualification for advanced therapies over a 4-year period (2019–2022).

The exclusion criteria were:

1. No history of dopaminergic medication intake prior to admission to clinic
2. Signs of atypical parkinsonism and need for further evaluation and observation
3. Medical history recorded in hospital's database insufficient to be evaluated by researchers via tools used in this study.

The data was acquired retrospectively from the Silesian University Hospital Neurological Unit's anonymised database.

All clinicians assessing the patients were neurologists specialised in movement disorders, with > 5 years' experience in the diagnosis and treatment of aPD including the available DAT.

All participants were assessed with 5-2-1 criteria based on the reported intake of oral L-dopa, the presence of > 2 h of waking time in the 'OFF' state, and troublesome dyskinesia reported by the patient during interview, and confirmed in a history chart review.

Furthermore, every patient was evaluated using the MANAGE-PD instrument at www.managepd.com based on information about the presence and severity of additional clinical features such as unpredictable motor fluctuations, dystonia with pain, hallucinations without insight, freezing of gait, impulse control disorder, incidence of falls, and impaired ADL [8, 9]. Subsequently, all patients were divided into two subgroups, the first being classified into MANAGE-PD '1' and '2' categories meaning not needing DAT at the time of evaluation, and a second subgroup '3' signifying possible benefit from DAT according to the tool's assessment.

Data concerning different types of dopaminergic medications taken by patients was gathered and for each sample a levodopa equivalent daily dose (LEDD) [11] was measured, as well as MDS-UPDRS part III score in both 'ON' and 'OFF' states and H&Y staging.

Additionally, information about the patient's gender, domicile (rural or urban), occupation, the presence of a caregiver, as well as information about the type of clinician who referred the patient to the clinic was collected and analysed.

Statistical analysis was performed with Statistica 13.3 software (TIBCO Software Inc. 2017). http://statistica.io). Quantitative variables were presented as an arithmetic mean and standard deviation (normally distributed variable) or median and interquartile range (variables with skewed distribution). Qualitative

variables were presented as absolute values and percentages. The normality of distribution was assessed with the Shapiro–Wilk test.

Data without confirmation of the normal distribution in the analysed groups was assessed with a Mann–Whitney U-test, a Fisher's exact test or a chi-square test. A p-value below or equal to 0.05 was considered statistically significant. Odds ratios (ORs) with a 95% confidence interval (CI) and *p* values were obtained using binary logistic regression. The variables that were significantly associated with the univariate logistic regression were then analysed using multivariate logistic regression. The significance level was set at $p < 0.05$.

Results

The study group consisted of 260 patients diagnosed with Parkinson's Disease, referred by general neurologists for qualification to DAT in a tertiary neurology clinic in 2019 to 2022 inclusive: 51 (19.5%) met all three of the 5-2-1 criteria, and 123 (47.1%) patients were categorised as '3' in MANAGE-PD, meaning that they might benefit from DAT. Finally, at the local centre level, 64 (24.5%) patients were qualified for DAT. 22 (34.4%) patients who were qualified for DAT by a clinician did not meet the 5-2-1 criteria. All these patients were selected by MANAGE-PD. Only one patient qualified for DAT therapy did not meet either the 5-2-1 or the MANAGE-PD criteria.

The 5-2-1 scheme based on the data from this study was characterised by a 92.5% specificity level and a 65.1% sensitivity level compared to 69.5% specificity and 98.4% sensitivity levels of MANAGE-PD.

Detailed data is set out in Table 1.

Study group with regard to MANAGE-PD qualification:

There were no significant differences regarding residence, gender or age at assessment between patients qualified and not qualified by MANAGE-PD to DAT.

The group of patients classified by MANAGE-PD to DAT was characterised by a longer disease duration (12.4 ± 6.2 vs 5.7 ± 4.5 years, p = 0.0000); and worse motor status both in the 'OFF' (MDS-UPDRS p.III OFF 49 vs 33 points, p = 0.0000) and 'ON' states (MDS-UPDRS p.III ON (23 vs 17 points, p = 0.0000). Among qualified patients, motor fluctuations both predictable (81.3 vs 15.4%, p = 0.0000) and unpredictable (58.5 vs 9.6%, p = 0.0000) were much more common. These patients were also more likely to report that the symptoms of the disease affected their daily activities (42.3 vs 29.4%, p = 0.0000).

Characteristics of dopaminergic treatment in all subjects were gathered and compared between groups determined by MANAGE-PD assessment.

The group of patients classified as '3' by MANAGE-PD was characterised by higher average LEDD, had received more levodopa doses, had a longer history of levodopa usage, and a higher number of antiparkinsonian medications. In these subjects, dopamine agonists, amantadine and COMT-I were used significantly more often, whereas MAOB-I usage was not statistically different in both groups.

Detailed data is set out in Table 2.

Factors determining qualification

Multivariable logistic regression analysis was performed based on the univariate logistic regression results to identify predictors of qualification in patients with PD. The number of levodopa doses, and the presence of predictive fluctuations were identified as predictive factors for qualification, however the absence of unpredictable fluctuations and time with troublesome dyskinesias decreased the likelihood of qualification.

A second model was performed to identify within the group qualified by MANAGE-PD the predictive factors for qualification to DAT in the further assessment by clinicians. The number of levodopa doses, MDS-UPDRS part III in the 'OFF' state, and the presence of motor fluctuation were identified as predictive factors.

The results are set out in Table 3.

Table 1. Data regarding qualification

	Whole group	5-2-1	Manage-PD	Qualified by clinician
n	261 (100%)	51 (19.5%)	123 (47.1%)	64 (24.5%)
True positive	64 (100%)	41 (80.0%)	63 (51.2%)	64 (100%)
False positive	197 (75.5%)	10 (19.6%)	60 (48.8%)	
False negative	0 (0%)	22 (34.4% of qualified)	1 (1.5% of qualified)	
True negative	0 (0%)	200 (76.6% of all subjects)	137 (52.5% of all subjects)	
Sensitivity	100%	65.1%	98.4%	
Specificity	0%	95.2%	69.5%	
5-2-1 Delphi criteria				
Criteria of 5	119 (45.6%)	51 (100%)	103 (83.7%)	57 (89.1%)
Criteria of 2	128 (49.0%)	51 (100%)	118 (95.5%)	61 (95.3%)
Criteria of 1	63 (24.1%)	51 (100%)	64 (52.0%)	43 (67.2%)

Table 2. Demographic and clinical data with characteristics of parkinsonian treatment of patients qualified and disqualified by MANAGE-PD

	'1' or '2' in MANAGE-PD	'3' in MANAGE-PD	P-value
Age (years) mean ± SD	68.5 ± 14.8	68.7 ± 16.9	0.7856
Gender n (%)			0.2363
Male	77 (56.6)	76 (61.8)	
Female	59 (43.4)	47 (38.2)	
Residence n (%)			0.1670
Rural area	12 (8.8)	20 (16.3)	
Town/city	123 (90.2)	100 (83.7)	
Age at PD onset (years) Mean ± SD	62.9 ± 10.4	56.3 ± 10.7	0.0000
Duration of disease (years) Mean ± SD	5.7 ± 4.5	12.4 ± 6.2	0.0000
MDS-UPDRS p. III OFF (points) [IQR]	33 [21–45]	49 [35–65]	0.0000
MDS-UPDRS p. III ON (points) [IQR]	17 [8–24]	23 [14–33]	0.0000
Hoehn-Yahr (points) [IQR]	2 [2–3]	3 [3–4]	0.0003
'OFF' state > 2h n (%)	18 (13.2)	110 (89.4)	0.0000
'ON' state with troublesome dyskinesias n (%)	4 (2.9)	62 (50.4)	0.0000
Predictable fluctuations n (%)	21 (15.4)	100 (81.3)	0.0000
Unpredictable fluctuations n (%)	13 (9.6)	72 (58.5)	0.0000
Impact of symptoms on ADL	40 (29.4)	52 (42.3)	0.0211
LEDD (mg) [IQR]	443 [188-769]	1,365 [900–1,793]	0.0000
Levodopa doses			
[IQR]	3 [2–4]	6 [5–6]	0.0000
> 5 doses of levodopa n (%)	14 (10.30)	103 (83.7)	0.0000
Duration of levodopa usage (years)	2.5 [1–6]	10 [7–13]	0.0000
Medication: n (%)			
Dopamine agonists	60 (44.1)	83 (67.5)	0.0007
Amantadine	12 (8.8)	39 (31.7)	0.0000
MAOB-I	29 (21.3)	24 (19.5)	0.5255
COMT-I	1 (0.7)	6 (4.9)	0.0454
Number of antiparkinsonian medications	2 [2–3]	2 [1–2]	0.0000

Table 3. Predictors for qualification to DAT by clinicians and predictors of qualification to DAT by clinicians in patients qualified to DAT by MANAGE-PD

Predictors for qualification to DAT by clinicians				
	OR	95% CI		P-value
Levodopa doses	0.60385	0.2096	0.9981	0.002683
Predictable fluctuation	1.32783	0.26224	2.39341	0.014594
Absence of unpredictable fluctuation	–0.65306	–1.10457	–0.20154	0.0004585
Time with troublesome dyskinesias (> 1h)	–1.16828	–1.61495	–0.72161	0.000000

Predictors of qualification to DAT by clinicians in patients qualified to DAT by MANAGE-PD				
	OR	95% CI		P-value
Levodopa doses	0.4124	0.03805	0.78674	0.030835
MDS-UPDRS p.III 'OFF'	0.03557	0.00916	0.06198	0.008287
Predictable fluctuation	1.25619	0.14689	2.36549	0.026452
Unpredictable fluctuation	–0.63719	–1.06291	–0.21146	0.003352

Discussion

In its late stages, Parkinson's Disease becomes especially hard to manage as the severity of the symptoms rises while the medication effectiveness diminishes [7, 14, 25].

With device-aided therapies having been proved to have a positive impact in slowing the progression of overall disability, the challenge is to find those patients who may benefit from the treatment as early as possible. Substantial efforts have been put into defining the criteria for the disease to become adequately described as advanced Parkinson's Disease, which ultimately could be used interchangeably with DAT eligibility [15–18, 24].

On the other hand, with growing accessibility to the therapies and rising awareness among both practitioners and patients, there is a risk of too many incorrectly diagnosed with advanced PD patients being referred to specialised movement disorders centres, thus delaying the admission of really DAT-eligible patients. In accordance with Antonini et al.'s validation paper, in our study the patients disqualified from DAT by MANAGE-PD showed lower clinical burden, and scored lower on almost all measures, suggesting that these patients were in an earlier stage of PD. Additionally, most of the them lacked motor fluctuations and dyskinesia which implies the absence of a 'narrow therapeutic window', suggesting oral medications might still be sufficient [8].

An important detail was brought up by H.R. Moes in his letter to the editor of the aforementioned study, pointing out that the percentage of DAT-eligible patients was high (50%) in their study compared to the 26% in daily practice of general neurologists (GNs) treating PD patients. In the cohort analysed by our team, the results were similar (46% eligible for DAT), which indicates comparable limitations due to differences in the population we tested. It may be possible that this deviation is due to a proportion of patients being 'filtered out' by the GNs as outpatients and not being admitted to the PD clinic in the first place. Nevertheless, it may have an effect of lowering the number of false-positive patients found and thus hindering evaluation of the accuracy of the predictive value [18, 20].

In the study by Malaty et al, in which a positive result of the 5-2-1 algorithm was defined as meeting at least one of the criteria, only 78.6% of physician-classified aPD patients were 5–2-1 positive. In this study, we assumed that being positive equated to meeting all three criteria, which substantially increased the sensitivity of the tool [3].

It has been noted that patients which were 5-2-1-negative and described as aPD were substantially more burdened by non-motor symptoms which, while not covered by 5-2-1 criteria, are included in MANAGE-PD. Our study seems to support this finding of 'falsely negative' patients as all the patients attributed to DAT by clinicians in our centre were accurately assigned with the MANAGE-PD tool [3].

The data suggests that even when applying a stricter approach to assigning the former tool's subgroups, MANAGE--PD has a clear advantage in terms of screening virtually every aPD patient as indicated by this scoring system.

Additionally, in this study we found MANAGE-PD would allow lowering the number of patients primarily directed for evaluation for DAT by 52.9%, which shows potential for reducing healthcare resource use (HCRU) and lessening the caregiver burden.

It is worth noting that in the aforementioned study by Malaty et al. [3] the reference was a clinical diagnosis of advanced Parkinson's Disease. Although this is often used interchangeably with DAT eligibility, this might lead to confusion as understanding of the term still varies among clinicians. As Antonini et al. stated in their research, only 34.5% of patients qualified for advanced treatment were diagnosed by clinicians with aPD [9]. That unfortunately further impedes collating these two studies, despite promising results [5].

For years, researchers have been seeking the most reliable clinical characteristics that may be included in screening tools concerning PD [5].

The results of our study are consistent with the characteristics of patients diagnosed with aPD in the literature [1, 5, 19].

Positive predictive factors corresponding with the ultimate qualification made by PD specialists identified in this study were: MDS-UPDRS part III score when assessed in the 'OFF' state, the amount of daily L-dopa doses, and the presence of motor fluctuations, while the absence of unpredictable fluctuations was found to be a negative predictor for qualification.

Compellingly, > 2 h of waking time in the 'OFF' state was not a predictive factor, which may suggest that only the presence of both the 'OFF' state and dyskinesia result in positive qualification due to a suspected possible 'narrow therapeutic window' being one of the main reasons for using DAT. In this context, the absence of dyskinesia in patients experiencing the 'OFF' state may be understood as insufficient oral L-dopa intake [12, 13]. Additionally, correlation of daily L-dopa doses suggests a general loss of drug effectiveness that combined with the abovementioned symptoms are distinctive features of advanced Parkinson's Disease. [25]

In addition, the MDS-UPDRS score in the 'ON' state was found to not correlate with admission to DAT, which suggests that MDS-UPDRS p. III scale has limited potential when solely used to assess disease progression, an observation which is consistent with findings from other trials regarding this topic [23, 26, 27].

Limitations

There are various limitations regarding our study.

It is clear that our study is limited by accepting clinicians' judgment as the reference to both tools analysed. However, the multifaceted context of both Parkinson's Disease presentation and its interaction with a patient's comorbidities and general condition means that still today no other method of DAT qualification is superior to man-made assessment.

The process of retrospective data analysis may to some degree influence the use of both tools, as researchers used information reported by PD specialists in patient charts without being able to examine the patients themselves. Furthermore, depending on patient-reported data, especially considering measuring them in the context of their severity required for MANAGE-PD, is freighted with the possibility of inaccuracies given the multitude of variables collected.

Taking all this into account, the 5-2-1 criteria have the clear advantage of being simpler and capable of swift completion even while having limited data about a patient in assessment.

Another limitation is that patients with signs of atypical parkinsonism were not included in this study, which may in theory be important for general neurologists who may use the tools to evaluate such patients they encounter in their daily practice. It is important to note that as patients with atypical parkinsonism are generally not susceptible to DAT, analysing them with tools designed for PD patients may produce confusing results [20]. It is also important to highlight that both the presence of the 'OFF' state and the presence of troublesome dyskinesia were assessed based on reports collected from patients by clinicians, rather than acquired using a Parkinson's Disease home diary such as that drawn up by Hauser et al. [28].

Conclusions

In our study we found that MANAGE-PD has a better screening potential of DAT admission than 5-2-1 criteria. While both tools are reliable and valuable in daily practice, our study suggests that some patients may be missed when using only the less complicated tools during the assessment.

Future directions

Considering only a moderately sized group of patients was included in this trial, further efforts need to be made in order to provide sufficient data regarding this topic.

Due to the retrospective character of the work and data anonymisation, there was no requirement to obtain ethical approval for this study by the Ethics Committee.

Article information

Conflicts of interest: *None.*
Funding: *This publication was prepared without any external source of funding.*

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