Accepted: 28 January 2018

DOI: 10.1111/coa.13082

ORIGINAL ARTICLE

WILEY

Voice quality outcomes of idiopathic Parkinson's disease medical treatment: A systematic review

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Introduction: To investigate voice quality (VQ) impairments in idiopathic Parkinson's disease (IPD) and to explore the impact of medical treatments and L-Dopa challenge testing on voice.

Methods: Relevant studies published between January 1980 and June 2017 describing VQ evaluations in IPD were retrieved using PubMed, Scopus, Biological Abstracts, BioMed Central and Cochrane databases. Issues of clinical relevance, including IPD treatment efficiency and voice quality outcomes, were evaluated for each study. The grade of recommendation for each publication was determined according to the Oxford Centre for Evidence-Based Medicine evidence levels.

Results: The database research yielded 106 relevant publications, of which 33 studies met the inclusion criteria, for a total of 964 patients with IPD. Data were extracted by 3 independent physicians who identified 21, 11 and 1 trials with IIIb, IIb and IIa evidence levels, respectively. The main VQ assessment tools used were acoustic testing (N = 27), aerodynamic testing (N = 10), subjective measurements (N = 8) and videolaryngostroboscopy (N = 3). The majority of trials (N = 32/33) identified subjective or objective VQ improvements after medical treatment (N = 10) or better VQ evaluations in healthy subjects compared to patients with IPD (N = 22). Especially, our analysis supports that VQ overall improves during the L-Dopa challenge testing, making the VQ evaluation an additional tool for the IPD diagnosis. The methodology used to assess subjective and objective VQ substantially varied from 1 study to another. All of the included studies took into consideration the patient's clinical profile in the VQ analysis.

Conclusion: The majority of studies supported that VQ assessments remain useful as outcome measures of the effectiveness of medical treatment and could be helpful for the IPD diagnosis based on L-Dopa challenge testing. Further controlled studies using standardised and transparent methodology for measuring acoustic parameters are necessary to confirm the place of each tool in both IPD diagnosis and treatment evaluation.

B. Harmegnies and S. Saussez Contributed equally to this work and should be regarded as joint last authors.

1 | INTRODUCTION

Idiopathic or primary Parkinson's disease (IPD) is one of the most prevalent progressive neurodegenerative diseases, affecting approximately 8-18 per 100 000 person-years in industrialised countries.[1,2] Beyond the classical motor symptoms and signs, 70%-89% of patients develop voice disorders at baseline[3,4] or during disease progression along with motor disability progression.[5,6] The occurrence of voice quality alterations is well known to negatively impact patient quality of life, leading to the development of communicative disabilities,[7] depression and patient isolation.[8] Therefore in the last 2 decades, an increasing number of studies have evaluated voice quality impairments at baseline (the time of initial diagnosis) and throughout the progression of IPD. Most studies found substantial differences between patients with IPD and healthy subjects at the time of diagnosis;[7,9-11] however, controversy still persists with regard to the impact of medical treatment on voice quality.[10,12,13] This point is particularly important because an increasing number of trials tend to use voice quality as an outcome measure of treatment effectiveness.[12,14]

In addition, to date, the IPD diagnosis remains clinical and needs, in some cases, the use of dat-scan or L-Dopa challenge testing, which is interesting to assess the effectiveness of L-Dopa on the motor state of the patient.[15] However, the assessment of the efficiency of L-Dopa during the L-Dopa challenge testing is subjective and based on the clinical examination of the neurologist (ie walking test). In this context, a significant number of studies have been conducted to use voice quality as precise tool able to objectify the efficiency of the L-Dopa intake during the L-Dopa challenge testing.[9,14]

The aim of this review was to investigate both voice quality differences between healthy subjects and patients with IPD and the impact of both medical IPD treatments and L-Dopa challenge testing on voice quality. This study does not focus on the effect of Lee Silverman Voice Therapy® on voice quality. Thus, trials in which patients received voice therapy were excluded. The review was conducted according to the PRISMA checklist for reviews and meta-analyses.[16]

Keypoints

- IPD patients have more voice quality impairments than healthy controls at baseline and throughout the course of the illness.
- The administration of L-Dopa during the challenge testing seems to improve aerodynamic and/or acoustic measurements.
- Majority of trials studying the impact of L-Dopa on voice quality of patients with IPD had poor to modest quality of evidence, had unclear inclusion and exclusion criteria, had small numbers of patients and did not take into consideration the various patient profiles.
- There is no placebo randomised controlled trial interesting to the impact of L-Dopa on voice quality in IPD.
- The heterogeneity between studies with regard to the tools and methods used to assess voice quality prevents the identification of the most interesting parameters to use in future as outcome of the treatment efficiency or the IPD evolution.

2 | MATERIALS AND METHODS

2.1 | Types of studies, participants/problem, outcomes, comparison and interventions

2.1.1 | Selection of patients

In this review, we focused on trials studying patients with a clear diagnosis of IPD based on neurological symptoms and signs (optionally underpinned by Hoehn and Yahr scale, Unified Parkinson's disease rating scale (UPDRS) or other tools), a suitable positive dat-scan result, positive L-Dopa test and/or the exclusion of Parkinson Plus Syndrome. The authors had to exclude some cofactors perturbing voice assessments (ie upper aerodigestive tract infections in the previous month, severe addiction to tobacco or alcohol and other identifiable causes of laryngitis).[17] The symptoms and signs recorded consisted of clinical surveys or simply history/observation(s) made by the practitioner. In addition, the authors had to assess the subjective and/or objective voice quality of subjects with IPD using validated tools.

2.1.2 | Intervention of interest and comparison between IPD and healthy subjects

Two groups of cohort studies were included. The first group included case-controlled studies comparing patients with IPD (ON or OFF state) with healthy subjects. The second group included randomised, prospective/retrospective, controlled/uncontrolled studies, evaluating the evolution of voice quality in patients with IPD along treatment or during the ON/OFF testing (L-Dopa challenge testing).

2.1.3 | Outcomes

In both groups of studies, subjective and/or objective voice quality has been assessed in all subjects. The methodological procedures used for voice quality assessments were analysed for the following evaluations:

1. Subjective voice quality: tools, evaluation method (unique, multiple blinded/unblinded judge(s)) and speech material (phonetic text, sustained vowels, etc.);
2. Aerodynamic measurements: measures assessed and whether a calibrated machine was used;

3. Acoustic measurements: software, vowel characteristics (choice, condition of speech (normal intensity), duration, vowel sample number recorded and analysed), utilisation of a microphone and the vowel sample portion on which the acoustical measurements were obtained.

In addition, the effect of L-Dopa (or other) on voice quality was assessed in each prospective study taking into account all the characteristics of the trial.

2.2 | Ethical consideration

The present review entitled "Voice quality outcomes of idiopathic Parkinson disease medical treatment: a systematic review" receives the agreement of the Ethical Committee of EpiCURA Hospital (P2013/010).

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2.3 | Search strategy

A literature search was conducted to identify articles related to IPD voice quality published in English, French and other languages between January 1980 and June 2017. The databases searched were Biological Abstracts, BioMed Central, Cochrane, PubMed/Medline and Scopus. Various keywords were used, including: "Parkinson," "Parkinsonism," "Idiopathic," "Primary," "Voice," "Speech" and "Degenerative." We identified the multiple inclusion cases by checking age, sex, author and geographic area whenever these data were available.

2.4 | Data selection, extraction and analysis

The research protocol, data selection, extraction and analysis were developed a priori. Three independent authors (JRL, VR and SB) screened and selected each study with available abstracts, full texts or titles referring to IPD. They evaluated the papers for the following characteristics: (i) patient characteristics (N, age, sex and disease state); (ii) diagnosis method, (iii) inclusion and exclusion criteria; (iv) adequacy of the process of allocation and comparability of randomised groups; (v) risk of epidemiological bias; (vi) treatment features; (vi) follow-up time; (vii) clinical and voice quality outcomes used; and (viii) method used to assess voice quality. The grade of recommendation (ranging from Ia to V) was determined for each paper according to the Oxford Centre for Evidence-Based Medicine evidence levels.[18] Risk of bias was assessed using the Tool to Assess Risk of Bias in Cohort Studies (TARBCS) developed by the Clarity Group and Evidence Partners.[19]

3 | RESULTS

3.1 | Search results

The initial search identified more than 400 references from the 5 databases. Abstracts of these references were screened, and a total of 127 studies had the potential to meet our selection criteria (106 relevant papers from PubMed, 11 publications from Scopus, 8 publications from BioMed Central, 2 publications from Cochrane Library database and no relevant publications from Biological Abstracts; Table 1). From this primary identification and after the analysis of the full-text articles, we selected 33 pertinent publications that included a total of 964 patients with IPD (Figure 1). Among these 33 articles, we found 22 controlled studies accounting for 720 patients with IPD and 10 prospective case series describing 244 patients. Two studies[13,20] were simultaneously case-controlled and prospective studies and were classified in the second group. Figure 1, Tables 2 and 3 provide a detailed description of all the included studies.

3.2 | Patient characteristics, treatments and follow-ups

Data related to age and sex were reported in 32 and 30 of the 33 studies, respectively (Tables 2 and 3). Women accounted for 34.96% of all patients, and the average patient age was 64.59 years (ranging from 43 to 84 years). At the time of assessment, the mean values of the Hoehn and Yahr scales and UPDRS were 2.20 and 26.46, respectively, and the duration of disease was 5.50 years. In therapeutic studies, we identified 4 different medical regimens: L-Dopa alone (N = 17); L-Dopa + other drug(s) (ie anticholinergics, amantadine, bromocriptine, ergot-type medication, amphetamines, catecholamines catabolism inhibitors) (N = 4); other drugs alone (N = 3); and medication ± surgical procedures (ie pallidotomy (N = 1) or bilateral subthalamic stimulation [N = 3]). In this case, we only focused on data concerning the effect of medical treatment on voice quality. Concerning the ON/OFF trials, the mean time without drugs before the examination was 10.67 hours (8-12 hours) and the mean time between the L-Dopa intake and assessment of the drug's effect was 75 minutes (30-120 minutes).

3.3 | Diagnosis and clinical outcomes

IPD diagnosis was based on the clinical judgement of the physician in all publications. The Hoehn and Yahr scale alone (N = 14) and the

TABLE 1 Result of the literature search

Database	Publications found	Publications selected
PubMed	106	33
Scopus	11	0
BioMed Central	8	0
Biological Abstracts	0	0
Cochrane	2	0

The database search results found 106 relevant publications in PubMed, 11 relevant publications in Scopus, 8 publications in BioMed Central, 2 relevant publications in Cochrane Library and any publication in Biological Abstracts.

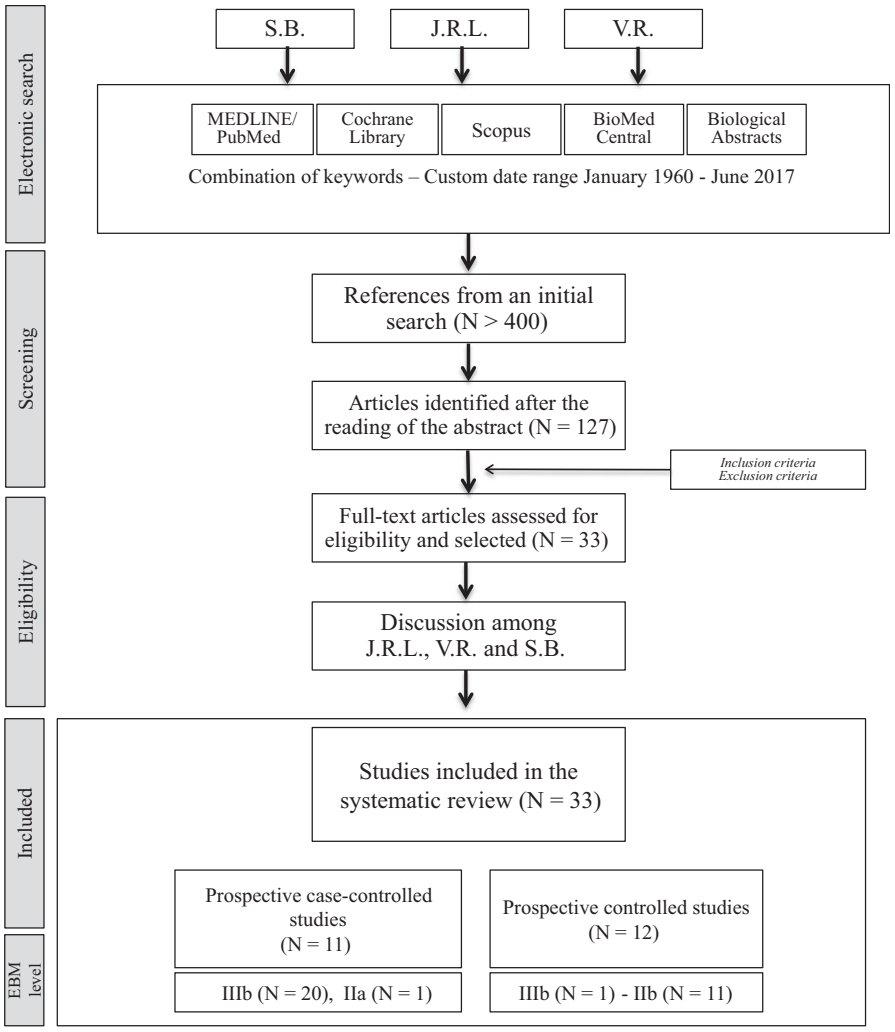

FIGURE 1 Flow chart describing the process of article selection for this study

UPDRS (N = 8) were the most common clinical scale used for patient follow-up after treatment.

3.4 | Voice quality outcomes

Fourteen case-controlled trials assessed voice quality only with objective measurements; 1 trial used only subjective assessment; and 7 trials used both subjective and objective evaluations. Concerning the secondary identification group, 9 trials used objective assessments and 2 studies considered subjective and objective voice quality evaluations.

Of these 33 studies, 1 patient-based subjective instrument (Voice Handicap Index (VHI), N = 4) and 2 clinician-based subjective instruments (Grade, Roughness, Breathiness, Asthenia, Strain [GRBAS] [N = 6] and Speech/Voice score [N = 2]) were used (Table 4). Among the objective voice quality outcomes, acoustic parameters were used in 27 studies, aerodynamic measurements in 10 studies, videolaryngostroboscopy (VLS) findings in 3 studies and an electromyography study in 1 trial (Tables 2 and 3 [online]).

Respecting the acoustic measurements, the utilisation of a microphone varied from 1 study to another (Tables 2 and 3). MDVP® (Kay Elemetrics Corp., NJ, USA) was the most frequently used software to measure acoustic parameters (N = 7/21), followed by Computerized Speech Lab® (KayPentax, NJ, USA) (N = 7), Praat® (University of Amsterdam, the Netherlands) (N = 3) and C-Speech® (C-Speech, WI, USA) (N = 2). There was significant variability between studies according to the vowel used to measure acoustic parameters. Eighteen studies measured acoustic parameters on a sustained/a/, 4 studies used the vowel/i/, and 4 studies used at least 2 different vowels. One trial used connected speech. The duration of the sustained vowel and the sample number recorded and analysed varied from 1 study to another. The sustained vowel duration ranged from 2 seconds to the maximum phonation time. The number of recorded samples ranged from 1 to 6 samples, and the portion of the recording on which acoustic cues were measured varied from 1 study to another:

1. No information provided about the portion of the recording on which acoustic cues were measured (N = 11);
2. Measurement on the most stable portion of the signal (1, 2 or 3 seconds) without a clear definition of the "most stable portion" (N = 4);

TABLE 2 Overview of study designs, patient characteristics, inclusion criteria and assessment tools of the selected case-control studies

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
Murdoch, et al[41]	Controlled	IIIb	Gr1: 19 IPD "ON"	1. Clinical diagnosis of IPD	Vital capacity	Abnormal: 4/19	/a/,/i/,/u/; no statistic available	L-Dopa±
			Gr2: CT	2. Duration: 4-15 y	MPT	Gr2 > Gr1		Anticholinergics±
			Sex & age:	3. Hoehn and Yahr: 3-5	Forced Expiratory Volume 1 s	Abnormal: 5/19		Amantadine
			Gr1: 68 ± 7.3 y (56-82 y)					
			13M-6F					
Zwirner, et al[58]	Controlled	IIIb	Gr1: 18 IPD	1. Clinical diagnosis of IPD	Jitter	Gr2 > Gr1	Microphone use: 15 cm	L-dopa
			Gr2: CT	2. Hoehn and Yahr: 1-3	Shimmer	Gr1 = Gr2	/a/—MPT duration	
			Sex & age:		SNR	Gr1 = Gr2	Sample number recorded: several	
			Gr1: 6F, 12M		F0	Gr1 = Gr2	S. portion choice: mid-4 s < 5 first s	
			Gr1: 68 y (56-81 y)		STD	Gr2 > Gr1	C-Speech	
Hertrich I, et al[23]	Controlled	IIIb	Gr1: 24 IPD	1. Clinical diagnosis of IPD	MF0	M: Gr2 > Gr1	Microphone use: 5 cm	L-Dopa
			Gr2: 25 CT	2. Voice deterioration		F: Gr1 = Gr2	/a/—4-s duration	
			Sex & age:		Jitter	M: Gr2 > Gr1	Sample number recorded: 3	
			Gr1: 9F, 15M			F: Gr1 = Gr2	Sample number analysed: 3	
			F: 64 y, M: 65 y		Shimmer	Gr1 = Gr2	S. Portion choice: 1 s stable	
			Gr2: 25, 13F, 12M		HNR	Gr1 = Gr2	Quiet room—CSL Laryngograph	
			F: 57 y, M: 52 y					
Jimenez-Jimenez[9]	Controlled	IIIb	Gr1: 22 IPD "OFF"	1. Clinical diagnosis of IPD	F0	Gr2 > Gr1	Microphone use: 8 cm	None
			Gr 2: 28 CT	2. Duration: 2.5 ± 2.3 y	Jitt	Gr2 > Gr1; Gr1 = Gr2 (F)	/a/—NP duration	
			Sex & age:	3. UPDRS: 17.6 ± 9.5	ShdB	Gr2 > Gr1; Gr1 = Gr2 (F)	Sample number recorded: 3	
			M: 65.3 ± 12.5	4. Hoehn and Yahr: 1.9 ± 0.4	HNR	Gr1 = Gr2; Gr2 > Gr1 (M)	Sample number analysed: NP	
			F: 62.8 ± 12.1		STD	Gr2 > Gr1; Gr1 = Gr2 (F)	S. portion choice: 2 s stable	
			Gr1: 12M-10F		SD intensity	Gr1 = Gr2	Quiet room—CSL	

(Continues)

TABLE 2 (Continued)

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
			Gr2: 16M-12F		MPT	Gr1 = Gr2		
					phonational range	Gr1 = Gr2		
					s/z ratio (M)	Gr1 = Gr2; Gr2 > Gr1		
					VLS		Not blinded	
					laryngeal tremor	Gr2 > Gr1		
					glottal closure degree	Gr1 = Gr2		
					hyperphonation	Gr1 = Gr2		
					Loudness, monopitch, harshness	Gr2 > Gr1		
					arrest, tremor	Gr2 > Gr1		
					Pitch breaks, struggle	Gr1 = Gr2		
Gamboa, et al[52]	Controlled	IIIb	Gr1: 41 IPD "ON"	1. Clinical diagnosis of IPD	Microphonic signal/a/		Microphone use: NP	L-Dopa (N = 37)
			Gr2: 28 CT	2. UPDRS: 24.3 ± 14.5	F0	Gr1 > Gr2	/a/—2 s	Bromocriptine/
			Sex & age:	3. Hoehn and Yahr: 2.29 ± 0.71	Jitter	Gr1 > Gr2	Sample number recorded: 3	Ergot-type medication
			69.8 y	4. Duration: 4.80 y ± 3.50	Shimmer	Gr1 = Gr2	Sample number analysed: NP	(N = 35)
			24M-17F		HNR	Gr1 = Gr2	S. portion choice: 2 s stable	Selegiline (N = 7)
			Gr2: 16M-12F		SD intensity	Gr1 = Gr2	Quiet room: CSL—Laryngograph	Anticholinergics(N = 1)
					Phonational range	Gr1 < Gr2		Amantadine (N = 1)
					Dynamic range	Gr1 = Gr2		
					MPT	Gr1 = Gr2		
					S/Z ratio	Gr1 = Gr2		
Holmes, et al[4]	Controlled	IIIb	Gr1: 30 early stage IPD	1. IPD early stages	pitch	Gr1 = Gr2	/a/	Medication (N = 48)
			Gr2: 30 later stage IPD	2. IPD later stages	Jitter	G1, 2 > G3	Microphone use: 1 cm	Drug: NP
			Gr3: 30 CT	3. MMSE: normal	high-speaking F0	G1, 2 > G3 (M)	/a/—NP duration	No treatment (N = 12)
			Sex & age:	4. Beck: normal	reduced F0 variability	G1, 2 > G3 (F)	Sample number recorded: NP	
			Gr1: 68.4 y (50-81 y)	5. Mean duration Gr1: 2.4 y			Sample number analysed: NP	
			Gr2: 74.5 y (63-81 y)	6. Mean duration Gr2: 13.2 y			/a/—4-s duration (jit, shim, NHR	
					breathiness	Gr1 > Gr2	Quiet room—CSL	

(Continues)

TABLE 2 (Continued)

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
Yuceturk, et al[53]	Controlled	IIIb	Gr1: 30 IPD	1. Clinical diagnosis of IPD	MF0	Gr2 > Gr1	Microphone use: 20-30 cm	L-DopaN.A.
			Gr2: 20 CT	2. UPDRS: 54.7 (7-73)	Maximum F0	Gr2 > Gr1	/a/—5-s duration	
			Sex & age:		Minimal F0	Gr2 > Gr1	Sample number recorded: NP	
			Gr1: 64.6 y		Range of frequency	Gr2 > Gr1	Sample number analysed: NP	
			14M-16F		Intensity	Gr2 > Gr1	S. portion choice: 2 s middle	
			Gr2: 9M-11F		HNR	Gr2 > Gr1	Quiet room	
			57.7 y		MPT	Gr2 > Gr1		
					VLS	aN=21/30	/a/maximum I and F0 Dr Speech	
					Irregular VF edge	3		
					Posterior glottal chink	4		
					Anterior glottal chink	2		
					Decreased mucosal wave	6		
					No mucosal wave	3		
					Phase asymmetry	3		
					Aperiodicity	3		
					Thick mucoid secretion	3		
Oguz, et al[59]	Controlled	IIIb	Gr1: 14 IPD	1. Clinical diagnosis of IPD	MF0	Gr1 = Gr2	Microphone use: 8 cm	
			Gr2: 22 CT	2. No voice complaint	Shim	Gr1 = Gr2	/a/—NP duration	
			Gr1: 14F		Jitter	Gr2 > Gr1	Sample number recorded: 3	
			65.79 ± 10.63 y		Loudness	Gr2 > Gr1	Sample number analysed: 1	
			Gr2: 22F		HNR	Gr2 > Gr1	S. Portion choice: 3 s middle	
							Quiet Room—Praat	
Zarzur, et al[21]	Controlled	IIIb	Gr1: 26 IPD "ON"	1. Clinical diagnosis of IPD	Laryngeal EMG hypertonicity	Gr>Gr2 (wrong)	vowel:/i/(low & high pitch)	N.A.
			Gr2: 26 presbyphonia	2. Vocal complaints	Thyroarytenoid & cricothyroid	Gr1 = 73%	Duration: 10 to 15 s	
			Sex & age:	3. Duration: 6.32 (1-15 y)	Voice rest	Gr 2 = 23%		
			Gr1: 68.8 (58-81)					

(Continues)

TABLE 2 (Continued)

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
				4. Hoehn and Yahr: 2.07 (1-4)				
			18M-8F					
			Gr2: N.A.					
Rahn, et al[60]	Controlled	IIIb	Gr1: 41 IPD	1. Clinical diagnosis of IPD	Per cent jitter	Gr2 > Gr1		Medication
			Gr2: 40 CT			M: Gr2 > Gr1	Microphone use: 15 cm	Drug: NP
			Gr1: 20F, 21M			F: Gr1 = Gr2	/a/—3-s duration	
			F: 60 ± 10.97, M: 56 ± 8.58		Per cent shimmer	Gr1 = Gr2	Sample number analysed: 3	
			Gr2: 22F, 18M			M: Gr1 = Gr2	S. portion choice: 1 s central	
			F: 51 ± 6.48, M: 42 ± 11.90			F: Gr1 = Gr2		
Midi, et al[3]	Controlled	IIIb	Gr1: 20 IPD "ON"	1. IPD early	Roughness	Gr2 > Gr1 (M)	Standard reading text	Medication
			Gr2: 20 CT	2. Duration: 1-5 y	Breathiness	Gr2 > Gr1	2 ENT & 2 speech pathologist	Drug: NP
			Sex & age:	3. motor UPDRS: 14.65 ± 6.55	Asthenia	Gr2 > Gr1	Blinded	
			Gr1: 61.5 y		VHI	Gr2 > Gr1		
			12M, 8F		Jitter	Gr1 = Gr2	Microphone use: 10 cm	
			Gr2: 10M-10F		Shimmer	Gr1 = Gr2	/a/—5-s duration	
					NHR	Gr1 = Gr2	Sample number recorded: NP	
					F0	Gr1 = Gr2	Sample number analysed: NP	
					vF0	Gr1 > Gr2 (M)	S. portion choice: NP	
							Quiet room—MDVP	
					MPT	Gr2 > Gr1	MPT: 3 times/a/	
					Non-closure glottic (VLS)	Gr1 = Gr2		
Rusz, et al[61]	Controlled	IIIb	Gr1: 46 IPD "OFF"	1. Clinical diagnosis of IPD	STD	Gr1 = Gr2	Microphone use: 15 cm	None
			Gr2: 23 CT	2. Duration Gr1: 30 m	Jitt	Gr2 > Gr1	/i/—MPT duration	
			Sex & age:	3. Hoehn and Yahr: 1-2	RAP	Gr2 > Gr1	Sample number recorded: 1	
			Gr1: 61.7 y		PPQ5	Gr2 > Gr1	Sample number analysed: 1	
			19M-4F		Jitter DDP	Gr2 > Gr1	S. portion choice: NP	

(Continues)

TABLE 2 (Continued)

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
					Shim	Gr2 > Gr1	Quiet room	
					APQ3	Gr2 > Gr1		
					APQ5	Gr2 > Gr1		
					APQ11	Gr2 > Gr1		
					Shimmer DDA	Gr2 > Gr1		
					NHR	Gr2 > Gr1		
					HNR (dB)	Gr2 > Gr1		
Bauer, et al[7]	Controlled	IIIb	Gr 1: 21 IPD "ON"	1. Clinical diagnosis of IPD	VHI	Gr2 > Gr1	1 examiner, not blinded	Medication
			Gr 2: 21 CT		G, R, B, S, I	Gr2 > Gr1		Drug: NP
			Sex & age:		A	Gr2 = Gr1		
			Gr1: 72 y		Highest F0	Gr2 = Gr1	with a stroboscope	
			11M, 10F		lowest frequency	Gr2 = Gr1		
			Gr2: 10M-11F		Voice range	Gr2 > Gr1		
					jitter	Gr2 = Gr1		
					shimmer	Gr2 = Gr1		
					MPT	Gr2 > Gr1		
					s/Z	Gr2 = Gr1		
					Videolaryngostroboscopic:			
					mucosal wave abnormalities	Gr1:17/21; Gr2: 8/21		
					laryngeal tremor	Gr1: 6/21, Gr2: 0/21		
					non-closure glottis pattern	Gr1: 11/21, Gr2: 6/21		
Tanaka, et al[62]	Controlled	IIIb	Gr1: 15M IPD "ON"	1. Clinical diagnosis of IPD	Grade of dysphonia (M)	1.29	3 experienced speech therapists	L-Dopa
			Gr2: 24F IPD "ON"	2. Duration:	Grade of dysphonia (F)	0.96	Book passage	2 h after medication
			Gr3: 33M CT	M: 44.6 ± 29.7 y	Jita	Gr3 > Gr1; Gr4 > Gr2	Microphone use: NP	
			Gr4: 29F CT	F: 46.9 ± 35.7 y	Jitt	Gr3 > Gr1; Gr4 > Gr2	/a/—<5-s duration	
			Sex & age:		RAP	Gr3 > Gr1; Gr4 > Gr2	Sample number recorded: NP	
			M: 72.5 y±7.6 (58-80)		PPQ	Gr3 > Gr1; Gr4 > Gr2	Sample number analysed: NP	

(Continues)

TABLE 2 (Continued)

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
			F: 69.5 y± 7.3 y (53-78)		sPPQ	Gr3 > Gr1; Gr4 > Gr2	S. portion choice: NP	
					vF0	Gr3 > Gr1; Gr4 > Gr2	Quiet room NP—MDVP	
					Shdb	Gr3 > Gr1; Gr4 > Gr2		
					Shim	Gr3 > Gr1; Gr4 > Gr2		
					APQ	Gr3 > Gr1; Gr4 > Gr2		
					sAPQ	Gr3 > Gr1; Gr4 > Gr2		
					vAm	Gr3 > Gr1; Gr4 > Gr2		
					DVB, NVB	Gr1 = Gr3; Gr2 = Gr4		
					DSH, NSH	Gr1 = Gr3; Gr2 = Gr4		
					DUV, NUV	Gr1 = Gr3; Gr2 = Gr4		
					NHR	Gr3 > Gr1; Gr4 > Gr2		
					VTI	Gr3 = Gr1; Gr4 > Gr2		
					SPI	Gr3 > Gr1; Gr4 > Gr2		
					FTRI	Gr3 > Gr1; Gr4 > Gr2		
					ATRI	Gr1 = Gr3; Gr2 = Gr4		
					Fftr	Gr3 > Gr1; Gr4 = Gr2		
					Fatr	Gr1 = Gr3; Gr2 = Gr4		
Graças, et al[30]	Controlled	IIIb	Gr1: 19F IPD "ON"	1. Clinical diagnosis of IPD	Sustained/a/		3 speech therapist	L-dopa
			Gr2: 27F CT		G, R, I	Gr2 > Gr1	Not blinded	

(Continues)

TABLE 2 (Continued)

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
			Sex & age:	2. Diagnosis with BB UKPD	B, A, S	Gr1 = Gr2		
				3. Hoehn and Yahr: 1-3				
			66 y (62-74 y)		Perceptual connected speech:			
					G, R, I	Gr2 > Gr1	Microphone use: NP	
					B, A, S	Gr1 = Gr2		
					F0	Gr1 = Gr2		
					Per cent jitter	Gr2 > Gr1	/a/—NP duration	
					PPQ	Gr2 > Gr1	Sample number recorded: NP	
					Per cent shimmer	Gr1 = Gr2	Sample number analysed: NP	
					APQ	Gr1 = Gr2	S. portion choice: NP	
					HNR	Gr1 = Gr2	Quiet room—CSL	
Silva, et al[31]	Controlled	IIIb	Gr 1: 27 IPD "ON"	1. Clinical diagnosis of IPD	G, B, I	Gr2 > Gr1	counting 1-20 and days of week	L-dopa ±
			Gr2: 27 CT	2. Hoehn and Yahr: 1-3	R, A, S	Gr1 = Gr2	4 blinded speech therapists	Ergot-type medication
			Sex & age:		F0	Gr2 > Gr1	Microphone use: NP	Amantadine
			Gr1: 59.96 y (39-79)		Jitter	Gr2 > Gr1	/a/—NP duration	CCI
			Gr1: 27M		Shimmer	Gr1 = Gr2	Sample number recorded: NP	Anticholinergics
			Gr2: 27M		NHR	Gr2 > Gr1	Sample number analysed: NP	Selegiline
							S. portion choice: NP	Bromocriptine
							Quiet room—MDVP	
Lazarus, et al[6]	Controlled	IIIb	Gr1: 66 IPD UPDRS < 45	1. IPD diagnosis with UKPD	MF0	Gr1 = Gr2	Microphone use: NP	Medication
			Gr2: 67 IPD UPDRS>45	Brain Bank Diagnosis Criteria	Mean Loudness	Gr1 = Gr2	NP speech sample	Drug: NP
			Gr1: 13F, 53M	2. Hoehn and Yahr Gr1: 1.9 ± 0.6	Inability to make Z (s/Z ratio)	Gr1 > Gr2	Sample number analysed: NP	
			52.96 y	Hoehn and Yahr Gr2: 2.7 ± 0.4	S/Z ratio	Gr1 > Gr2	S. portion choice: NP	

(Continues)

TABLE 2 (Continued)

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
			Gr2: 9F, 58M		Mean diadochokinetic rate	Gr1 = Gr2	Vaghmi speech and voice system	
			60.73 y					
Bang, et al[63]	Controlled	IIIb	Gr1: 7 IPD	1. Clinical diagnosis of IPD	/a/		Microphone use: 5 cm	Medication
			Gr2: 7 CT	2. Duration: 3.57 ± 1.90 y	Per cent jitter	Gr2 > Gr1 (better)	/a//e/,/i/,/u/—5-s duration	
			Sex & age:	3. MMSE: 23.29 ± 3.73	Shimmer	Gr1 = Gr2	Sample number recorded: NP	
			Gr1: 7F	4. Hoehn and Yahr: 3.36 ± 1.11	NHR	Gr1 = Gr2	Sample number analysed: NP	
			68.43 ± 5.74 y		F1	Gr2 > Gr1 (better)	S. Portion choice: 1.5 s middle stable	
			Gr2: 7F		F2	Gr1 = Gr2	Quiet room—Praat	
					/e/			
					Per cent jitter	Gr2 > Gr1 (better)		
					NHR, Shimmer	Gr1 = Gr2		
					F1, F2	Gr1 = Gr2		
					/i/			
					Per cent jitter	Gr2 > Gr1 (better)		
					Shimmer, NHR	Gr1 = Gr2		
					F1, F2	Gr2 > Gr1 (better)		
					/u/			
					Per cent jitter, NHR	Gr2 > Gr1 (better)		
					Shimmer	Gr1 = Gr2		
					F1, F2	Gr1 = Gr2		
Tykalova, et al[54]	Controlled	IIIb	Gr1: 20 IPD	1. Clinical diagnosis of IPD	pitch	Gr1 = Gr2	Microphone use: 15 cm	None
			Gr2: 16 CT	2. Hoehn and Yahr: 2.2 ± 0.5	intensity	Gr1 = Gr2	Short block of text	
			Gr1: 20M	3. UPDRS: 17.8 ± 7.2	duration	Gr1 = Gr2	5 similar sentences	
			60.5 y (34-82 y)	4. Native Parkinsonian	Stress Pattern Index	Gr2 > Gr1	Quiet room—Praat	
			Gr2: 16M		Pitch Range	Gr2 > Gr1		

(Continues)

TABLE 2 (Continued)

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
Ikui, et al[11]	Controlled	IIIb	Gr1: 30 IPD "ON"	1. Clinical diagnosis of IPD	Highest F0	Gr2 > Gr1	phonation time: 6 times	L-dopa
			Gr2: 30 CT	2. Hoehn and Yahr: 2.7 ± 0.8	Lowest F0	Gr1 = Gr2 (F)	conversational pitch & loudness (2x)	
			Sex & age:	3. UPDRS: 38 ± 17		Gr2 > Gr1 (M)	highest pitch, lowest pitch, loudest and softest voice: 1 trial for each	
			M: 73.1 y (61-80)		Pitch range	Gr2 > Gr1		
			F: 73.8 y (61-80)		Intensity	Gr1 = Gr2		
			Gr1: 15M, 15F		Mean flow rate	Gr1 = Gr2		
					Expiratory pressure	Gr1 = Gr2		
					MPT	Gr1 = Gr2		
Silbergleit, et al[64]	Controlled	IIa	Gr1: 21 Mild OFF-IPD	1. Clinical diagnosis of IPD	Semi-tone range	Gr3 > Gr2; Gr3 > Gr1 (M)	Microphone use: 6.3 cm	L-Dopa
			Gr2: 13 Moderate OFF-IPD				/i/—3-s duration	
			Gr3: 32 CT				Sample number recorded: NP	
			Gr1: 6F, 15M				Sample number analysed: NP	
			Gr2: 2F, 11M				S. portion choice: 1 s middle	
			Gr3: 10F, 22M					
			Gr1: 61.1 y±5.2 y					
			Gr2: 66.1 y±9.5 y					
			Gr1: 63.8 y±9.0 y					
Van Hooren, et al[22]	Prospective Uncontrolled	IIIb	Gr1: 100 IPD	1. Clinical diagnosis of IPD	VHI	>10 (94%)		Drugs at least 12 h
			Gr1A: 27 H&Y1	2. Voice and swallowing disorders	VHItot	Gr1A>1B>1C>1D		
			Gr1B: 31 H&Y2		VHIe	Gr1A>1B>1C>1D		
			Gr1C: 21 H&Y3		VHIf	Gr1A>1B>1C>1D		
			Gr1D: 21 H&Y4		VHIp	Gr1A=B=C=D		
			27F-73M		Visual Analogue Scale Voice	Gr1A>1B>1C>1D		
			67 y		Voice-related QoL	Gr1A>1D; Gr1B>1D		

CCI, catecholamine catabolism inhibitor; CT, control; ENT, ear-nose-throat; EMG, electromyography; F1, formant 1; F2, formant 2; F, female; GRBASI, grade, roughness, breathiness, asthenia, strain, instability; IPD, idiopathic Parkinson's disease; M, male; MDVP, multidimensional voice programme; MPT, maximum phonation time; NA, not available; NP, not provided; QoL, quality of life; SNR, signal-to-noise ratio; UPDRS, Unified Parkinson Disease Rating Scale; VHI(f, e, p, tot), voice handicap index functional, emotional, physical, total score; VLS, videolaryngostroboscopy; y, year.
The grade of recommendation (ranging from Ia to V) was determined for each paper according to the Oxford Centre for Evidence-Based Medicine evidence levels.[18]

TABLE 3 Overview of study designs, patient numbers, inclusion criteria, treatment outcomes, therapeutic procedures and follow-up period of the selected prospective trials

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
Poluha, eta l.[27]	Prospective ON/OFF	IIb	Gr1: 10 IPD "ON" Gr1: 10 IPD "OFF"	1. Clinical diagnosis of IPD	MPT of/i/ MPT of/u/ MPT of/ae/	Gr1 > Gr2 Gr1 > Gr2 Gr1 > Gr2		L-dopa (30 min)
Jiang, et al[44]	Prospective ON/OFF	IIb	Gr1: 15 IPD "ON" Gr2: OFF at least 8 h Sex & age: Gr1: 67 ± 7.7 (47-82 y) 10M, 5F	1. Clinical diagnosis of IPD 2. Duration: 0.5 -10 y 2. Duration: 4.3 ± 3.1 3. Hoehn and Yahr: 2.7 ± 0.7 4. Webster scale: 11.2 ± 2.7 5. Tremor subscale: 1.1 ± 0.4	Jitter (%) Shimmer (%)	Gr1 = Gr2 Gr1 > Gr2 (better)	Microphone use: 15 cm /i/—2- to 3-s duration Sample number recorded: 3 Sample number analysed: NP S. portion choice: NP Quiet room: NP—C-Speech	L-dopa (45 m)
Goberman, et al[20]	Prospective Controlled ON/OFF	IIb	Gr1: 9 IPD "ON" Gr2: 9 IPD "OFF" Gr3: 8 CT Sex & age: 69.1 y (57-84) Gr1, 2: 6M, 3F Gr3: 5M, 3F	1. Clinical diagnosis of IPD 2. Duration: 11.4 y	F0	Gr1 > Gr2	Microphone use: 15 cm Rainbow Passage Reading Sample number recorded: NP Sample number analysed: NP S. portion choice: NP Quiet room—CSL	L-Dopa (N = 3) Ergot-type medication (N = 5) Selegiline (N = 2) Amantadine (N = 1) Anticholinergics (N = 1) CCI (N = 1) OFF: since 8 h ON: 1 h after drug
Sanabria, et al[50]	Prospective ON/OFF	IIb	Gr1: 20 IPD "ON" Gr2: 20 IPD "OFF" Sex & age: 10M-10F 63.5 y	1. Clinical diagnosis of IPD 2. Hoehn and Yahr: 2.38 ± 0.45 3. Duration: 7.00 y ± 3.72	F0 (increasing) Jitter Frequency Tremor Index VTI	Gr1 > Gr2 Gr1 > Gr2 Gr1 > Gr2 Gr1 > Gr2	Microphone use: 20 cm /a/—2 s Sample number recorded: 3 Sample number analysed: NP S. portion choice: low Jitt Quiet room: NP—MDVP	L-Dopa (120 min)
Mourao, et al[49]	Prospective ON/OFF	IIb	Gr1: 12 IPD "ON" Gr2: 12 IPD "OFF" Sex & age: 62.4 y (50-71)	1. Clinical diagnosis of IPD 2. Daily physical incapacity 3. Fluctuations/dyskinesias 4. 2) & 3) with drugs	F0 Jitter Shimmer PPQ	Gr 1 > Gr2 Gr1 = Gr2 Gr1 > Gr2 Gr1 = Gr2	Microphone use: 15 cm /a/—NP duration Sample number recorded: NP Sample number analysed: NP	Pallidotomy L-Dopa

(Continues)

TABLE 3 (Continued)

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
			5F-7M	5. Duration: 13.5 y	APQ	Gr1 > Gr2	S. portion choice: stable 3 s	
					NHR	Gr1 = Gr2	Quiet room: NP	
De Letter, et al[42]	Prospective ON/OFF	IIb	Gr1: 25 IPD "ON"	1. Clinical diagnosis of IPD	FVC	Gr1 > Gr2; M>F		OFF since 12 h
			Gr2: 25 IPD "OFF"	2. Duration: 5-14 y	MPT	Gr1 > Gr2	Sustained/a/	L-Dopa
			Sex & age:		PQ	Gr1 > Gr2; M>F		
			44-73 y				3 speech pathologists	
			16M-9F					
D'Alatri, et al[14]	Controlled Prospective ON/OFF	IIb	Gr: 12 IPD	1. Clinical diagnosis of IPD	UPDRS	Gr3 > Gr4 > Gr1 > Gr2		L-Dopa
			Gr1: Stim ON, Drug -	2. BS-Stimulation	Speech Score	Gr1 = Gr2 = Gr3 = Gr4	Reading task/conversation	Bilateral Subthalamic
			Gr2: Stim OFF, Drug -	3. Duration: 10-32 y	NHR	Gr1/Gr3 > Gr2/Gr4	Microphone use: 20 cm	Stimulation
			Gr3: Stim ON, Drug+		Per cent Jitter	Gr1/Gr3 > Gr2	/a/—5-s duration	
			Gr4: Stim OFF, Drug+		Per cent shimmer	Gr3 > Gr2	Sample number recorded: 3	
			Gr5: CT				Sample number analysed: 1	
			Sex & age:				S. portion choice: 3 s central	
			Gr1: 60.29 y (47-75 y)				Quiet room—MDVP	
			11M-1F					
Santos, et al[10]	Prospective Controlled ON/OFF	IIb	Gr1: 5 CT	1. Clinical diagnosis of IPD	G, R, B, A, S	Gr1 > Gr2, 3	3 speech therapists, not blinded	L-Dopa (30-60 min)
			Gr2: 5 IPD "ON"	2. Hoehn and Yahr: 2-3			Reading a text—MDVP	OFF: since 12 h
			Gr3: 5 IPD "OFF"	3. Duration: 1-18 y	F0	G1 = G2 = G3	/a/&/i/—MPT	Not blinded
			Sex & age:		Jitt	G1 = G2 = G3	Sample number recorded: 3	
			3M: 63.6 y (58-72)		Shim	G1 = G2 = G3	Sample number analysed: NP	
			2F: 60.0 y (48-72)		NHR	G1 = G2 = G3	S. portion choice: NP	
					VTI	G1 = G2 = G3	Quiet room	
Xie, et al[12]	Controlled Prospective ON/OFF	IIb	Gr1: 11 IPD "ON"	1. Clinical diagnosis of IPD	F0	Gr1 = 2=3 = 4=5 = 6=7	Microphone use: 4 cm	L-Dopa
			Gr2: "OFF" pre-surgery	2. Duration: 3-13 y	STD	Gr5 > Gr6 (F)	/a//i//u/—MPT duration	Bilateral Subthalamic
			Gr3: Stim ON, Drug -	3. BS-Stimulation	Jitt	Gr1 = 2=3 = 4=5 = 6=7	Sample number recorded: 3	Stimulation
			Gr4: Stim OFF, Drug -	4. UPDRS ON: 18-59	Shim	Gr1 = 2=3 = 4=5 = 6=7	Sample number analysed: NP	
			Gr5: Stim ON, Drug+	5. UPDRS OFF: 61-98	NHR	Gr1,2,3,5,7 > Gr6 (F)	S. portion choice: 3 s central	
			Gr6: Stim OFF, Drug+		vF0	Gr1 = 2=3 = 4=5 = 6=7	Quiet room—MDVP rapid repetitions of/pataka/	
			Gr7: 10 CT					
			Sex & age:					
			Gr1: 58.2 y (43-69 y)					

(Continues)

TABLE 3 (Continued)

References	Design	EL	Patients' characteristics	Inclusion criteria	Treatment outcomes	Results	Outcomes method assessment	Treatment type
			5M, 6F					
			Gr7: 4M-6F					
Mate, et al[48]	Prospective ON/OFF	IIb	Gr1: 25 IPD "OFF"	1. Advanced IPD	RAP	Gr2, 3, 4 > Gr1	Microphone use: NP	L-Dopa
			Gr2: 25 IPD "ON"	2. Duration: 13.7 ± 4.8 y	HNR	Gr1 = Gr2 = Gr3 = Gr4	Laryngograph	OFF: 12-h deprivation
			Gr3: 1 wk after surgery	2. Duration: 6-26 y	Shimmer	Gr2 > Gr1	/a/—NP duration	Subthalamic nucleus
			Gr4: 1 m after surgery		RAP (mic)	Gr1 = Gr2 = Gr3 = Gr4	Sample number recorded: NP	Stimulation
			Sex & age:		Shimmer (mic)	Gr1 = Gr2 = Gr3 = Gr4	Sample number analysed: NP	
			47 y±8.4 y		F0 (Lar)	Gr2 > Gr1	S. portion choice: NP	
			17M-8F		F0 (Mic)	Gr2 > Gr1	Quiet room: NP—CSL	
					Jitter (mic)	Gr1 = Gr2 = Gr3 = Gr4		
					Shimmer (mic)	Gr1 = Gr2 = Gr3 = Gr4		
Ghio, et al[13]	Controlled	IIb	Gr1: 29 IPD OFF	1. Clinical diagnosis of IPD	F0	Gr1 = Gr2	Microphone use: NP	L-Dopa
			Gr2: 29 IPD ON	2. Duration: 9 ± 5 y		Gr1 = Gr3	/a/—3-s duration	
			Gr3: 15 CT	3. UPDRS: 30.6 ± 10.2			Sample number recorded: NP	
			Gr1: 29M				Sample number analysed: NP	
			70.6 y				S. Portion choice: NP	

CCI, catecholamine catabolism inhibitor; CT, control; ENT, ear-nose-throat; EMG, electromyography; F1, formant 1; F2, formant 2; F, female; FVC, functional vital capacity; GRBASI, grade, roughness, breathiness, asthenia, strain, instability; IPD, idiopathic Parkinson's disease; M, male; MDVP, multidimensional voice programme; MPT, maximum phonation time; NA, not available; NP, not provided; QoL, quality of life; SNR, signal-to-noise ratio; PQ, phonatory quotient; UPDRS, Unified Parkinson Disease Rating Scale; VHI(f, e, p, tot), voice handicap index functional, emotional, physical, total score; VLS, videolaryngostroboscopy; y, year.

The grade of recommendation (ranging from Ia to V) was determined for each paper according to the Oxford Centre for Evidence-Based Medicine evidence levels.[18]

TABLE 4 Overview of the measurement instruments/tools on voice quality used in the selected studies

Outcomes	Tools	N
Subjective voice assessment		
Hetero-evaluation (GRBASI scale)	B	7
	G	5
	R	5
	A	5
	S	4
	I	3
Auto-evaluation	VHI	2
	Loudness	2
	Other	2
Objective voice assessment		
Acoustic parameters	Jitter	21
	Shimmer	19
	Signal-noise (HNR/NHR)	17
	F0	16
	PPQ	5
	VTI	5
	STD	4
	Highest F0	4
	MF0	4
	vF0	3
	Lowest F0	3
	RAP	3
	Intensity	3
	Pitch Range	2
	FTRI	2
	Semi-tone	2
	Dynamic range, Frequency Range	1
	sAPQ, vAm	1
	SPI, ATRI	1
	DVB, NVB	1
	DSH, NSH	1
	DUV, NUV	1
	Fftr, Fatr	1
	Reduced F0 variability	1
Aerodynamics	MPT	9
	S/Z	4
	Vital Capacity	2
	Mean Airflow Rate, PQ, FEV1	1
Video(strobo)laryngoscopy	VLS	4

A, asthenia; APQ, amplitude perturbation quotient; ATRI, Amplitude Tremor Intensity Index; B, breathiness; DSH, degree of subharmonics; DVB, degree of voice break; DUV, degree of unvoiced segment; F0, fundamental frequency; Fatr, amplitude frequency tremor; Fftr, fundamental frequency tremor; FEV1, forced expiratory volume in 1 s; FTRI, Fo-Tremor Intensity Index; G, grade of dysphonia; I, instability; Jita, absolute jitter; Jitt, jitter per cent; MPT, maximum phonation time; NHR, noise harmonic ratio; NSH, number of subharmonics; NUV, number of unvoiced segment; NVB, number of voice break; PQ, phonatory quotient; PFR, phonatory fundamental frequency range; PPQ, pitch perturbation quotient; R, roughness; S, strain; ShdB, Shimmer; Shim, shimmer per cent; STD, standard deviation of F0; vF0, fundamental frequency variation; RAP, relative average perturbation; sAPQ, smoothed amplitude perturbation quotient; SPI, Soft Phonation Index; sPPQ, smoothed pitch perturbation quotient; vAm, peak-to-peak amplitude variation; VHI, voice handicap index; VLS, videolaryngostroboscopy; VTI, Voice Turbulence Index.

3. Measurement on the most stable portion of the signal (2 or 4 seconds) with a clear definition of the "most stable portion" (N = 2);
4. Measurement on the 1 to 3 central seconds of the signal (N = 7).

Many studies did not provide information regarding the software used, sample analysed and/or recorded and/or the utilisation of a microphone (Table 2 and 3).

3.5 | Methodological quality of the selected studies (evidence level) and bias

Our search found 21 trials with a IIIb evidence level, 11 studies with a IIb evidence level and 1 study with a IIa evidence level. We did not find any randomised placebo-controlled studies assessing the effect of L-Dopa on voice quality.

According to the risk of bias, firstly, the population of patients (neurological profile) varied considerably between studies, as 14 trials studied all IPD stages, 7 studies focused on early/mild or moderate or severe stages of IPD, and the remaining studies (N = 11) did not provide clear information about the stage IPD evaluated. In addition, in 3 studies,[21–23] patients were recruited on the basis of the occurrence of a perceptual voice disorder, which constitutes a selection bias limiting the comparison with the other studies. With regard to the patient profiles, another bias was a lack of information contained in the IPD patient profiles (ie trembling or akinetic) composing the studies. In fact, 30 studies (N = 30/33) did not precisely identify the patient profiles at baseline or mixed the different IPD profiles. This point is crucial as it has been suggested that the expression/profile of the patient with IPD may impact the development of some voice disorders over others.[7,24]

Secondly, sampling bias was present in many cohort studies due to inadequate or a lack of exclusion criteria. A total of 11 studies did not provide information regarding the exclusion criteria or did not assess cofactors that may have impacted the voice assessment (ie smoking, alcohol consumption, laryngopharyngeal reflux) that may have led to confusion in the interpretation of the voice quality results.

Thirdly, it seems that several cross-sectional or prospective controlled studies (N = 16) did not statistically verify the comparability of the groups or did not provide information about the intergroup comparability. The remaining studies (N = 15) matched at least for gender or/and age of the patients.

Fourthly, with regard to perceptual voice quality assessment, disparities between the studies in the assessment of the GRBASI items also constitute bias, which leads to difficulties in comparing the results of the studies. Other observational biases may include i) the VLS material used (quality of pictures) and operator experience in detecting the presence of laryngeal abnormalities and ii) the lack of blinding.[3,9] In the same way, the main bias of studies measuring acoustic cues was the heterogeneity of the methods used to measure acoustic parameters which, as demonstrated in previous studies, may lead to different observations.[25]

3.6 | Voice quality evolution throughout L-Dopa challenge testing

At the exception of the study of Santos et al (conducted on only 5 patients) and the study of Ghio et al who only assessed F0, most of the trials studying voice quality along the L-Dopa challenge testing reported the improvement of, at least, 1 voice quality measurement after the L-Dopa intake (Table 3). More specifically, in studies that used acoustic parameters as treatment outcome, types of improved acoustic cues substantially vary between studies with a larger number of trials reporting a significant improvement in shimmer compared to jitter. Only 2 studies used aerodynamic measurements as voice quality outcome throughout the L-Dopa challenge testing;[26,27] and these 2 studies exhibited significant improvement in aerodynamic evaluations.

4 | DISCUSSION

Our systematic review included 33 publications from 1960 to 2017, covering a period of 57 years. As expected, most papers were published within the last 20 years, probably following the development of voice quality assessment technologies, which are increasingly available in most centres.

4.1 | Subjective voice quality assessments

Only a few controlled studies evaluated subjective voice quality impairments in IPD. The voice quality self-assessment approaches based on a standardised questionnaire are less dependent from the method used than self-evaluations based only on a practitioner's anamnesis.[28,29] It is thus easier to compare different studies observations to draw an overall conclusion. In this review, we only identified 2 trials comparing VHI between patients with IPD and healthy subjects. They found significantly better scores in controls,[3,7] suggesting a more apparent communication handicap related to voice disorders in patients with IPD.

Five controlled studies evaluated perceptual voice quality between patients with IPD and controls using the GRBASI scale.[3,4,7,30,31] The observations varied between studies even though the overall trend showed stronger scores in dysphonia, breathiness, roughness and instability in patients with IPD. Some well-known data support that methodology differences (ie blinded or unblinded evaluations, speech samples on which the evaluation is performed) between studies may influence intergroup differences.[32–34] To date, it remains difficult to draw clear conclusions even if patients with IPD are characterised using subjective voice quality alterations and compared to healthy subjects. Future standardisation is needed to improve the comparability between studies, especially with regard to perceptual voice quality assessment.

Another major point that is rarely taken into consideration in voice quality studies concerns the psychological condition of patients with IPD. Indeed, in previous phoniatric studies, depression, which

occurs in approximately 17% of patients with IPD,[35,36] is known to significantly impact the patient's voice and the subjective and objective voice quality measurements. Thus, interpretation of the results of the self-assessed voice quality questionnaires must carefully take into consideration the psychological state of the patient.

4.2 | Laryngeal evaluations

Several studies evaluating the laryngeal repercussions of the disease have found substantial findings. The most common laryngeal findings observed with videolaryngostroboscopic or high-speed camera examinations are glottal incompetence, characterised by disorders of vocal fold adduction and air leakage.[7,37,38] Vocal fold bowing, glottal tremors, midfold opening of the glottis on phonation, slowed vibration, increased phonation threshold pressure, chaotic vocal fold vibrations and paralysed vocal folds on examination have also been associated with IPD.[7,38–40] The VLS/high-speed camera examinations are important for better understanding of the pathophysiological mechanisms underlying voice disorders, but remain less underutilised in the studies described in this review (only 3 trials used these methods).[3,7,9] It should also be acknowledged that evaluation of laryngeal findings related to IPD must take into consideration the patient profile. Some laryngeal findings occur more frequently in patients with tremors than patients with an akinetic profile and vice versa.[24] In addition to the lack of VLS/high-speed camera utilisation, future studies must increasingly consider laryngeal findings related to the ageing voice. Indeed, many observable findings (ie glottal incompetence, glottal tremors) are often observed in patients suffering from an ageing voice. Thus, special attention must be paid to the selection of the control group and their laryngeal findings as related to presbyphonia.

4.3 | Aerodynamic measurements

The first study to evaluate modern aerodynamic measurements in IPD dates from the 1980s.[41] Since that time, controversy remains present. The most often assessed aerodynamic measurement is the maximum phonation time (MPT). This measure is easy to measure, and in the context of comfortable pitch and intensity, the method used to measure MPT does not significantly influence the result. Therefore, the volume was measured in 6 case-controlled studies[3,7,9,11,26,41] and 2 prospective studies (L-Dopa challenge testing).[27,42] The results observed in this review highlight the controversy, particularly in controlled trials, as half of the studies (N = 3/6) reported better MPT duration in controls compared to patients with IPD, and the remaining half did not find any differences (N = 3/6). In addition, according to previous studies of Poluha et al and De Letter et al, the administration of L-Dopa seemed to significantly improve MPT values, supporting a probable impact of L-Dopa on these measures.[27,42]

Interestingly, a few controlled studies simultaneously observed lower MPT values and non-closure glottis patterns (VLS) in some patients with IPD compared to controls, especially in patients with a tremor profile.[7,24] These data highlight that lower MPT values are mainly due to glottal incompetence. One possible hypothesis explaining the mixed aerodynamic results observed may be due to the different IPD patient profiles, which are often not taken into consideration in the results analysis. The main criticism imputed to the assessment of MPT remains the lack of consideration of vital capacity, which may substantially due to patient respiratory function, respiratory musculature illnesses, and, de facto, the IPD patient profile. Moreover, it is known that, in some disease states, patients with IPD may suffer from restrictive or obstructive lung deficits that substantially impact their vital capacity.[43]

For these reasons, it is recommended to use phonatory quotient (PQ; the ratio between vital capacity and MPT) to assess aerodynamic laryngeal function while taking into account the lung capacity of the patient. Other measurements, such as the mean flow rate or expiratory pressure, can be made, but their uses, especially in the context of the voice quality assessment, remain anecdotal in the current literature.[11] However, some studies assessed chest wall dynamics,[41] subglottal pressure, phonation threshold pressure,[44] lung, rib cage and abdominal volumes involved in speech[45] and laryngeal resistance[46] in the evaluation of the respiratory function and the speech rate in IPD. Among these controlled studies, Jiang et al[44] found a higher subglottal pressure in patients with IPD compared to healthy subjects who can have negative repercussions on the quality of the vibratory process of the vocal folds. The use of these measurements in a trial studying voice quality in IPD would be particularly meaningful.

In summarise, it remains very complicated to draw accurate conclusions about the impact of disease (and IPD treatment) on aerodynamic measurements leading to mixed results. Even if it seems highly probable that the disease has an impact on aerodynamic measurements by affecting both the lung and vocal functions, future studies using PQ, MPT and subglottic estimated pressure and taking into consideration the patient's IPD profile are needed.

4.4 | Acoustic measurements

Sixteen trials used acoustic measurements to differentiate patients with IPD from controls or as outcome measures of therapeutic efficiency. Acoustic analysis is a sensitive approach useful for detecting subtle functional alterations in the vibratory process of the vocal folds. However, the obtained results remain very dependent on the methodological approaches used to measure these parameters.[25,47] Overall, most controlled studies reported stronger values of some acoustic parameters in the IPD population compared to controls. In addition, the intake of L-Dopa during the challenge testing seems to be associated with an improvement in many acoustic values[12,14,20,44,48–50] that differ from 1 study to another. Regarding the high sensitivity of acoustic measurements and with regard to the impact of IPD on aerodynamic function, we support that L-Dopa could have a positive impact on acoustic parameters even if, to date, we are unable to clarify which are meaningful acoustic cues for treatment outcomes or for studying pathophysiology. The main explanation of these disparate acoustic results is found in the high

heterogeneity of the methods used to measure acoustic parameters. As described in many other phoniatric diseases,[25,32,51] it is crucial to standardise the methodological approach used to measure acoustic parameters, particularly microphone use, vowel choice and duration, sample number recorded and analysed, and vowel portions chosen for measurement. Moreover, as stated above, it seems that patients with an akinetic profile do not have the same neuromuscular dysfunction as patients with a trembling profile, leading to differences in chest (respiratory) and laryngeal muscular behaviours, and, de facto, in acoustic measurements. Therefore, it may be interesting to take into consideration the profile of the patients, the stage of disease and many common cofactors that influence voice quality (ie laryngopharyngeal reflux diseases, smoking, alcohol consumption).

4.5 | Transversal criticisms, future considerations and recommendations

To date, there are still a number of unanswered questions regarding voice disabilities in IPD. Voice impairments concern 70% to 89% of patients,[3,4] and it seems that both aerodynamic and acoustic measurements are useful to highlight the impact of L-Dopa on vibratory process of the vocal folds throughout the L-Dopa challenge testing or during the disease progression. The awareness of the methodological problem related to the measurement of acoustic parameters is particularly important to develop future studies interesting to the exact pathophysiological mechanisms underlying the development of the voice disorder in IPD, at baseline and along disease progression. With better comprehension of the pathophysiological process, we could discover better tools, useful for assessing treatment outcomes and disease progression.

4.6 | In summarise, to elucidate probative answers, future studies should consider some critical points:

Firstly, concerning inclusion and exclusion criteria, authors should carefully consider a maximum of general cofactors able to impact and bias the voice quality assessments (ie gender, age, smoking, alcohol consumption, laryngopharyngeal reflux, singing practice, sport).[51] More specifically, the knowledge of the clinical characteristics of the patients with IPD (ie axial or lateral motor impairments, disease stage, treatment used) makes sense for the interpreting of the dysphonia.[4] Secondly, with regard to the complexity of the mechanisms underlying the dysphonia involving muscular and neurological chest and laryngeal alterations, and dyskinesia related to L-Dopa, it seems important that the future studies assess voice quality with exhaustive subjective and objective evaluations including aerodynamic (PQ, MPT, subglottal pressure, voice intensity, etc.) and acoustic measurements. Voice intensity has been studied in trials interesting to speech dysfunction in IPD, but, to our knowledge, a few studies focusing on voice quality impairments evaluate this parameter, which seems however altered.[9,11,52-54] Concerning acoustic assessment, future researches need to standardise the method used to measure acoustic cues, or authors must carefully detail the methodology used to allow a comparability between some studies. As initially proposed by the Committee on Phoniatrics of the European Laryngological Society, we support the measurement of acoustic parameters on the sustained vowel/a/produced at comfortable pitch and intensity, 3 times, at maximal phonation time.[55] In addition, the acoustic measures could be made on the entire signal of the 3 vowels excluding the first and the last milliseconds of the onset and the end of the signal, which are unstable and improper for the current acoustic software (technical reason). We did not support the use of the most stable time intervals of 1, 2 or 3 seconds of the sustained vowel because that does not represent the voice of the patient compared to the entire signal of the vowel.[51] According to the abnormalities that can be found in these examinations,[39,53] it seems important to systematically perform a videolaryngostroboscopy or, when available, a high-speed camera examination. Thirdly, as indicated above, IPD patients have a higher risk of depression than healthy subjects, which is known to substantially impact voice quality evaluations with impaired subjective[8] and objective assessments,[56] leading to a misattribution of the cause of the dysphonia.[8,35,36,57] Finally, in the current literature, we did not found randomised placebo-controlled trials evaluating the impact of placebo vs L-Dopa on voice quality. Such randomised placebo-controlled trials could definitely demonstrate the impact of L-Dopa on voice quality in IPD.

5 | CONCLUSION

Firstly, results of this systematic review support that patients with IPD seem to have more voice quality impairments than healthy controls at baseline and throughout the course of the illness. Secondly, the administration of a standardised dose of L-Dopa seems broadly consistent with the improvement in objective voice quality measurements, without really having identified the most useful outcomes among aerodynamic and acoustic measures. However, our review highlights a number of limitations. On the 1 hand, the majority of trials conducted had poor to modest quality of evidence with unclear inclusion and exclusion criteria, had small numbers of patients and did not take into consideration the various patient profiles. On the other hand, the important heterogeneity between studies with regard to the tools and methods used to assess voice quality may limit the comparison across studies. Future studies using irreproachable epistemological analyses and as far as possible standardised multidimensional tools are needed to identify the pathophysiological mechanisms underlying the development of voice disability in IPD.

ACKNOWLEDGEMENTS

The authors would like to thank American Journal Expert for the proofreading of the manuscript. This research has been subsidised by the ARC N°AUWB-2012-12/17-UMONS convention from Communauté Française de Belgique.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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How to cite this article: Lechien JR, Blecic S, Huet K, et al. Voice quality outcomes of idiopathic Parkinson's disease medical treatment: A systematic review. *Clin Otolaryngol*. 2018;43:882–903. https://doi.org/10.1111/coa.13082