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Review Article

Consensus on the treatment of dysphagia in Parkinson's disease

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ABSTRACT

Background: Dysphagia is common in Parkinson's disease (PD). The effects of antiparkinsonian drugs on dysphagia are controversial. Several treatments for dysphagia are available but there is no consensus on their efficacy in PD.
Objective: To conduct a systematic review of the literature and to define consensus statements on the treatment of dysphagia in PD and related nutritional management.
Methods: A multinational group of experts in the field of neurogenic dysphagia and/or Parkinson's disease conducted a systematic evaluation of the literature and reported the results according to PRISMA guidelines. The evidence from the retrieved studies was analyzed and discussed in a consensus conference organized in Pavia, Italy, and the consensus statements were drafted. The final version of statements was subsequently achieved by e-mail consensus.
Results: The literature review retrieved 64 papers on treatment and nutrition of patients with PD and dysphagia, mainly of Class IV quality. Based on the literature and expert opinion in cases where the evidence was limited or lacking, 26 statements were developed.
Conclusions: The statements developed by the Consensus panel provide a guidance for a multi-disciplinary treatment of dysphagia in patients with PD, involving neurologists, otorhinolaryngologists, gastroenterologists, phoniatricians, speech-language pathologists, dieticians, and clinical nutritionists.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder with an estimated prevalence of 6.1 million individuals all over the world [1,2]. Dysphagia is common in PD, with a prevalence varying between 11% and 87% depending on the disease stage, the disease duration, and the assessing method [3,4]. All swallowing stages can be impaired by PD [5]. Mortality due to pneumonia is common [6,7]. Presence of dysphagia is associated with malnutrition risk and low energy intake in patients with PD [8–10].

The mainstream treatments for PD include dopaminergic medications and advanced therapies including infusions and deep brain stimulation [11]. Their efficacy on motor symptoms is widely recognized [12–14]. Conversely, the impact, either positive or detrimental, of PD treatments for swallowing impairments is still debated.

Several treatments options for dysphagia are currently available specifically targeting swallowing function. The main goals are to reduce morbidity and mortality associated with pulmonary infections and malnutrition and to maintain a satisfactory quality-of-life (QOL) [15]. Swallowing therapy, generally delivered by speech-language pathologists, aims to improve the safety and efficiency of swallowing by means of compensatory and rehabilitative strategies [16]. Neurostimulation techniques have been proposed for dysphagia treatment in adjunct to conventional swallowing therapy [17]. Alternative feeding methods are used in patients with severe dysphagia.

Unfortunately, limited and variable information exists as regards the efficacy, the timing, and the best approach for treatments of dysphagia in PD. Despite this, there is consensus on the importance of dysphagia care and referral to a dysphagia specialist as part of the routine clinical workup from the earliest stages of the disease [18,19].

Consensus-based processes are recognized through formal methodology to provide a guidance to clinicians in complex health issues in the absence of high-quality evidence. The methodology relies on definition of statements by the consensus of a panel of experts based on the best available evidence and the group's expertise [20].

In 2008, Dutch guidelines for speech and language therapy in PD have been developed and recently translated in English [21]. These guidelines provide evidence-based and detailed recommendations for swallowing therapy in patients with PD, but they reflected the specific context of the Netherlands and the literature search only covered publications until 2008. For this reason, we organized a Multinational Consensus Conference among experts aiming to provide clinical recommendations for physicians and allied health professionals to improve the management of patients with PD and dysphagia and support clinicians in clinical decision making. This manuscript reports the Consensus statements on treatments (PD treatments and dysphagia-specific treatments) and the role of nutritional management in patients with PD and dysphagia.

2. Materials and methods

The project was initiated by the Organizing Committee during the 2018 edition of the 'Dysphagia Update' Meeting, an international scientific event focused on neurogenic dysphagia that has been held biannually since 2008 under the patronage of the Italian Society of Neurology, the Italian Society of Neurorehabilitation, and the European Society for Swallowing Disorders. The Multinational Consensus Conference method was designed according to the US National Institutes of Health Consensus Development Program (http://consensus.nih.gov) [22] and the Methodological Handbook of the Italian National Guideline System [23].

The project covered a period of 36 months following five steps: (1) assignment phase, (2) scoping phase, (3) assessment phase, (4) face-to-face Consensus Conference, held on 27-28th September 2019, at the IRCCS Mondino Foundation, Pavia, Italy, and (5) update of the evidence (up to February 2021) and refinement of statements by e-mail.

The core of the consensus panel was formed by Italian neurologists who met regularly at the 'Dysphagia Update' meetings. Additional specialists, also from different medical disciplines and from other Countries were invited in order to achieve a broad geographic and multidisciplinary representation. Participants were selected based on their recognized involvement in the care of large cohorts of PD patients and/or their involvement in research projects on PD and/or neurogenic dysphagia, and/or because of their publication record on neurogenic dysphagia in peer-reviewed journals. Participants were invited by e-mail. A single reminder was sent to those who did not reply to the first invitation. The final group was made up of 21 neurologists, 4 otorhinolaryngologists (ear, nose and throat specialists - ENT), 3 phoniatricians, 2 gastroenterologists, 4 speech-language pathologists, 2 clinical nutritionists, 1 radiologist and a statistician.

In the **assignment phase,** four working groups were identified:

1. the Scientific Committee, comprising 7 members, planned and organized the whole project, selected the members of the other groups, and developed the questions following the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual

of the American Academy of Neurology (AAN) [24]. Clinically relevant questions were proposed by the Scientific Committee and discussed during several meeting according to the PICO format (Appendix 1);
2. the Technical Committee, comprising 6 members, systematically reviewed the evidence, organized the results into tables, and assisted the other working groups in all steps;
3. a Workgroup, comprising 9 members, provided the first draft of answers to the proposed questions prior to the Consensus Conference, based on personal expertise and the literature retrieved from the systematic review. The expert Workgroups, assisted by the Technical Committee and the Scientific Committee, summarized and critically integrated information from multiple sources, and presented findings of this activity during the Consensus Conference also pointing out research gaps and proposing topics for future research;
4. the Consensus Development Panel, comprising 6 members, was responsible for defining the presentation procedures and for the assessment of the final statements.

In the **scoping phase**, the procedure for the literature review and the protocol for the conference were defined. The Scientific Committee identified the topics and together with the Technical Committee formulated the questions to be addressed.

In the **assessment phase**, the Technical Committees carried out a systematic review to analyze the state-of-the-art on dysphagia in PD. The systematic review was reported according to PRISMA guidelines [25]. Studies eligible for inclusion were those dealing with screening, diagnosis, prognosis, treatment, and nutrition published since 1990, any kind of design and reporting original data on PD patients with dysphagia. Exclusion criteria were studies published in abstract form, case-reports, reviews, editorials, letters, studies on animals, studies including patients with dysphagia of mixed etiology. Results of the literature search on treatment and nutrition are presented in this manuscript, whereas those related to screening, diagnosis, and prognosis are reported in another paper [26]. Studies were identified from the National Library of Medicine's MEDLINE database, by means of specific search strategies, using a combination of exploded MeSH terms and free text (search strategy is reported in Appendix 2). Reference lists of identified articles were reviewed to find additional references. Records and full papers without electronic abstracts were reviewed independently by two reviewers to identify relevant studies. Disagreements were resolved by discussion between the two reviewers until consensus was reached. Studies were classified according to various descriptors, including topic, sample size, design, and level of evidence according to the AAN Classification of Evidence [24]. Each study was graded according to its risk of bias from Class I (highest quality) to Class IV (lowest quality). Risk of bias was judged by assessing specific quality elements (i.e., study design, patient spectrum, data collection, masking). The classification was performed by two reviewers, with disagreement resolved by discussion.

In consideration of the multidisciplinary expert groups and the generally low-level quality of evidence emerged from the systematic analysis of the literature, we adopted a modified Delphi method [24] to achieve consensus and develop the final statements. The method consisted in four subsequent rounds. The first one was performed electronically: a first set of statements were generated and sent by e-mail to the experts of the Workgroups. Answers were collected and analyzed to inform necessary changes. The second and the third rounds were carried out face-to-face, during the first and the second day of the Multinational Consensus Conference, respectively, with the participation of the entire panel. The fourth round was performed electronically: the final version of the statements, adapted, when required, according to the additional analysis of paper published since the consensus conference, was circulated by e-mail to the experts. On every round, a minimum of 80% agreement for each statement was required for inclusion in the final consensus statement (25/31).

Ultimately, the systematic literature analysis covered the period from January 1990 to February 2021.

3. Results

3.1. Questions of the consensus conference

The Scientific Committee formulated and submitted two questions on dysphagia treatments and two question on the nutritional management of patients with PD and dysphagia.

Questions on treatment:

a) What clinical and/or instrumental abnormalities require appropriate treatment?
b) What are the treatment options for dysphagia in PD (optimization of PD treatments, swallowing therapy, neuromodulation, medical treatments)?

Questions on nutrition.

a) What are the nutritional interventions for patients with PD and dysphagia?
b) When should percutaneous endoscopic gastrostomy be indicated for the nutrition of patients with PD and dysphagia?

3.2. Systematic review

The electronic search retrieved 747 citations and 8 additional papers were identified by manual search from the references of included reports (Fig. 1). A total of 174 papers met the inclusion criteria. Sixty-four papers dealt with dysphagia or nutrition in PD, but only 45 contained useful findings for elaborating the statements. The majority of studies were of Class IV. Most studies included <20 patients and had a pre-post design.

Table 1 summarizes the main characteristics of the studies retrieved during literature search (see Supplementary material for complete list of references); Table 2 depicts main information on the studies used as basis for the statements. Where there was no study was available to answer to the question, statements were entirely based on expert opinion and general literature on dysphagia and nutrition.

3.3. Treatment of dysphagia

Consensus statements on dysphagia treatment in patients with PD are reported in Box 1. Several swallowing abnormalities are reported in patients with PD [27–29]. Pharyngeal impairment leads to reduced swallowing safety, i.e., penetration/aspiration, which is associated with an increased risk of aspiration pneumonia [30]. Oral impairment is associated with longer meal duration, fatigue, and reduced swallowing efficiency, and it can lead to poor nutritional status [30] and impaired QOL [31]. Thus, both pharyngeal and oral impairments deserve prompt and appropriate intervention, regardless of the PD stage. As soon as an impairment of swallowing function is clinically or instrumentally detected across any stages of swallowing, the need of a dysphagia treatment should be considered. Swallowing treatment should be specific and guided by instrumental findings about dysphagia pathophysiology. Videofluoroscopic swallowing study (VFSS) and/or fiberoptic endoscopic evaluation of swallowing (FEES) should be used to identify pathophysiological mechanisms that guide the definition of swallowing treatment and to assess its efficacy [32]. Swallowing electromyography and high-resolution manometry may also be useful for guiding dysphagia treatment. Treatment of dysphagia in PD may rely on a range of interventions. Regardless of the severity of dysphagia and the treatments performed, oral care should be maintained in all patients with PD and dysphagia to reduce the rate of aspiration pneumonia, as suggested by general dysphagia literature [33,34].

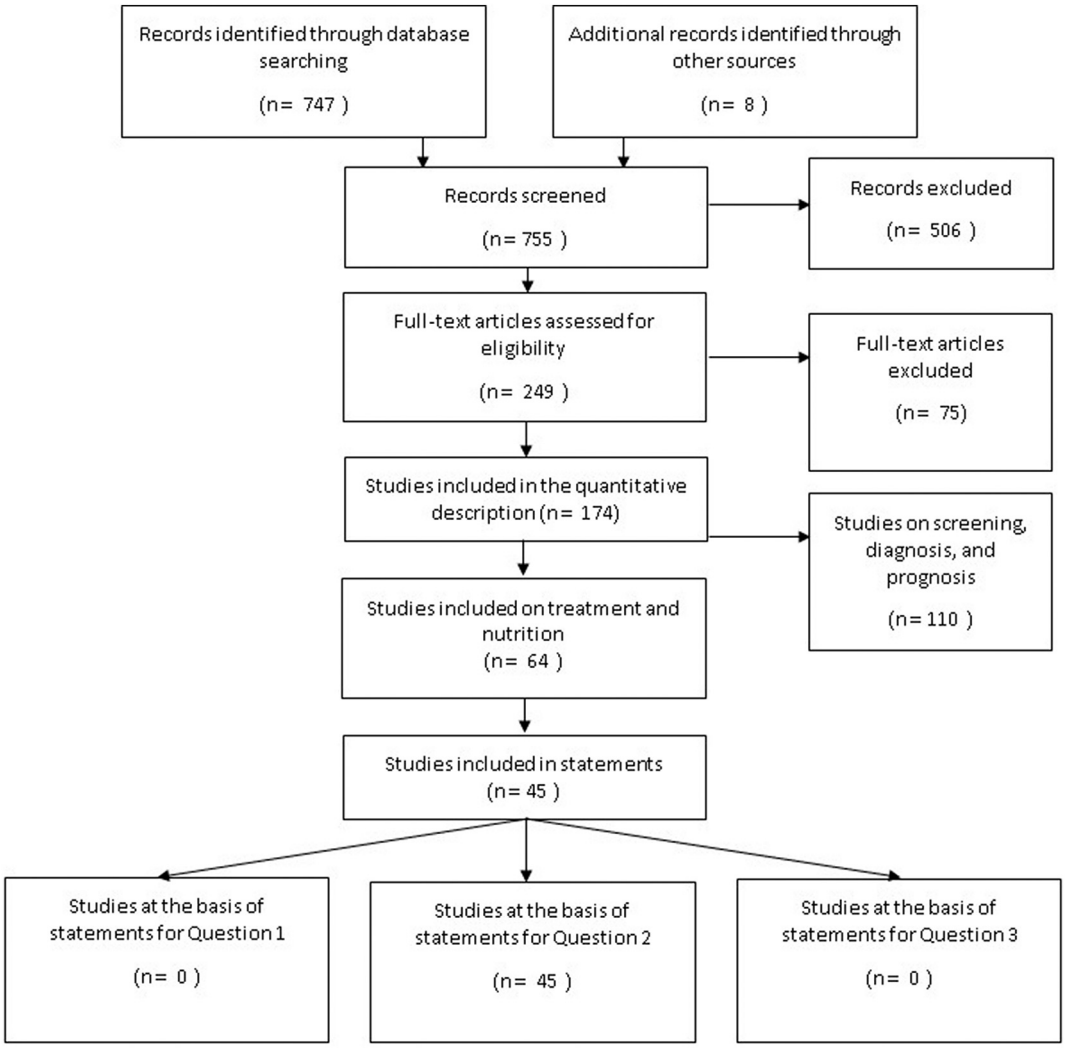

Fig. 1. PRISMA flow diagram.

Table 1
Descriptive features of eligible studies on the treatment and nutritional management of patients with PD and dysphagia.

	All studies	Number of patients = number of studies	Pre-post study	Non randomized CT	RCT	Cross-sectional study	Cohort study	Class of evidence
Topic	**N**	**N**	**N**	**N**	**N**	**N**	**N**	
Treatment	58	<10 pts. = 7 studies	41	2	14	1	–	3 Class I
		10–19 pts. = 22 studies						6 Class II
		20–50 pts. = 21studies						5 Class III
		>50 pts. = 8 studies						44 Class IV
Nutrition	6	<50 pts. = 1 study	–	–	–	5	1	2 Class I
		50–99 pts. = 2 studies						3 Class III
		>99 pts. = 3 studies						1 Class IV

Studies were classified according to various descriptors, including topic domain, sample size, design, presence of diagnostic criteria of the syndrome and level of evidence according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology [24]. Each study was graded according to its risk of bias from Class I to Class IV (with I being highest quality and IV lowest quality).
LEGEND. CT = controlled trial; RCT = randomized controlled trial.

3.3.1. Optimization of PD treatments

Treatment of PD rely on dopaminergic medications, infusion therapies and deep brain stimulation. Levodopa and dopamine replacement therapy is the gold-standard treatment for PD [35]. Dopaminergic treatment is known to improve motor function and pulmonary function tests (i.e. peak expiratory flow and upper-airway obstruction metrics) [12,36]. However, the effects on swallowing function are still debated. Based on the literature search, there is contradictory evidence that dopaminergic medications can improve or delay occurrence of dysphagia in PD. Few studies of Class III and IV with small sample size using different swallowing outcomes and short follow-up period have been conducted [37–43].

Some studies reported a beneficial effect of the levodopa-ON state on swallowing in about half of the patients with PD, regardless of the disease stage [37,38]. Dysphagia responsiveness to levodopa seemed to be related to dysphagia severity in the OFF-state [38]. Other studies

Table 2
Studies used as basis for the development of statements.

First author, y	Design	Treatment	N. patients	Level of evidence
Fuh, 1997	Pre-post study	Levodopa	19	IV
Hunter, 1997	Pre-post study	Levodopa	15	IV
Lim, 2008	Pre-post study	Levodopa	10	III
Michou, 2014	Pre-post study	Levodopa	26	III
Warnecke, 2016	Pre-post study	Levodopa	15	IV
Labeit, 2020	Pre-post study	Levodopa-carbidopa intestinal gel	11	IV
Ciucci, 2008	Pre-post study	DBS in STN	14	IV
Robertson, 2011	RCT	DBS in STN e GPi and Levodopa	27	II
Lengerer, 2012	Pre-post study	DBS in STN	18	IV
Sibergleit, 2012	Pre-post study	Bilateral DBS	14	IV
Wolz, 2012	Pre-post study	DBS in STN	34	IV
Troche, 2014	Pre-post study	Unilateral DBS in STN or Gpi	33	IV
Krygowska-Wajs, 2016	Pre-post study	Bilateral DBS in STN	20	IV
Sundstedt, 2017	Pre-post study	Bilateral DBS in cZI	9	IV
Olchik, 2018	Pre-post study	DBS (nfs)	10	IV
Xie, 2018	RCT (cross-over)	DBS in STN	11	II
Kawaguchi, 2020	Pre-post study	Bilateral DBS in STN	26	IV
Pflug, 2020	RCT (cross-over)	Bilateral DBS in STN vs combined STN + Substantia nigra-DBS	15	II
Luchesi, 2013	Pre-post study	Conventional swallowing therapy	24	IV
Manor, 2013	RCT	Conventional swallowing therapy vs video-assisted swallowing therapy	42	II
Luchesi, 2015*	Pre-post study	Conventional swallowing therapy	24	IV
Ayres, 2016	Pre-post study	Conventional swallowing therapy	11	IV
Wei, 2017	Non randomized CT	Out-of-hospital swallowing therapy	217	IV
Logemann, 2008	RCT (cross-over)	Chin-down posture, thickened liquids	360	III
Robbins, 2008	RCT	Chin-down posture, thickened liquids	255	I
Troche, 2008	RCT (cross-over)	Thickened liquids	10	IV
Nascimento, 2020	Pre-post study	Thickened liquids and Levodopa	50	IV
Ortega, 2020	Pre-post study	Thickened liquids	30	IV
Baert, 2021	Cross-sectional	Thickened liquids	83	III
Ayres, 2017	Non randomized CT	Chin-down posture	32	IV
Athukorala, 2014	Pre-post study	Skill-based swallowing training	10	IV
Sharkawi, 2002	Pre-post study	LSVT®	8	IV
Miles, 2017	Pre-post study	LSVT®	20	IV
Pitts, 2009	Pre-post study	EMST	10	IV
Troche, 2010	RCT	EMST	68	I
Byeon, 2013	RCT	EMST	33	IV
Troche, 2014**	Pre-post study	EMST	10	IV
Khedr, 2019	RCT	rTMS	33	I
Baijens, 2012	Pre-post study	TES	10	III
Heijnen, 2012	RCT	TES + standard swallowing therapy	109	IV
Baijens, 2013***	RCT	TES + standard swallowing therapy	109	II
Park, 2018	RCT	TES + standard swallowing therapy	18	IV
Alfonsi, 2010	Pre-post study	BT inoculation	7	IV
Alfonsi, 2017	Pre-post study	BT inoculation	12	IV
Howell, 2019	Pre-post study	Vocal fold augmentation	14	IV

* same study as Luchesi, 2013,**part of the patients from Troche 2010, ***same study as Heijnen, 2012.
Studies were classified according to various descriptors, including topic domain, sample size, design, presence of diagnostic criteria of the syndrome and level of evidence according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology [24]. Each study was graded according to its risk of bias from Class I to Class IV (with I being highest quality and IV lowest quality).
LEGEND. RCT = randomized controlled trial; LSVT® = Lee Silverman Voice Therapy®, EMST = expiratory muscle strength training; DBS = deep brain stimulation; STN = subthalamic nucleus; GPi = globus pallidus internal segment; cZI = caudal zona incerta; nfs = not further specified; rTMS = repetitive-transcranial magnetic stimulation; TES = transcutaneous electrical stimulation; BT = botulinum toxin.

reported small improvements in swallowing efficiency after levodopa administration in a certain percentage of patients with PD; however, this improvement did not reduce the rate and the severity of penetration and aspiration [39–42]. One study reported no effects of levodopa on bolus flow and swallowing biomechanics regardless of the bolus viscosity tested [43]. Finally, two studies reported detrimental effects of levodopa on swallowing function in about one in four patients [40,41]. The high variability of dysphagia response to levodopa suggests that swallowing abnormalities in PD are not solely related to dopamine deficiency [39].

Based on the literature, it is recommended to optimize the dopaminergic therapy in patients with PD and dysphagia, keeping in mind that the effects of this medications on swallowing function may either be beneficial or detrimental. In general, the timing of the administration of dopaminergic treatments should be planned so as to allow the patient to consume meals in the best ON-state. This means that patients should be advised to take levodopa-containing medications at least 30–60 min before meals [44,45], although more precise adjustments may be necessary on an individual basis. Dysphagia for medications is common in patients with PD, especially but not solely in the advanced stage [46]; therefore, patients' ability to swallow pills should be carefully investigated during instrumental assessment of swallowing, although the impact of dysphagia on dopaminergic response is still unclear [46,47].

Deep brain stimulation (DBS) is a widely used and accepted surgical procedure for the treatment of PD with motor fluctuations. Quadripolar electrodes are placed generally in the subthalamic nucleus (STN) or the globus pallidus internal segment (GPi). DBS has been reported to alleviate motor symptoms [13] and improve limb and motor control [14]. Results from studies on the effects of DBS on swallowing function are controversial. Twelve studies (3 Class II [48–50], 9 Class IV [51–59]) were retrieved from literature search. In the majority of the studies, DBS targeted the bilateral STN and was delivered with high frequency stimulation. Two studies compared the stimulation of the STN with the

Box 1
Statements on the treatment of dysphagia in PD.

A) What clinical and/or instrumental abnormalities require appropriate treatment?
Statements are based on expert opinion:

Ai. *Treatment should be started when there is clinical or instrumental evidence of impairment of swallowing safety and/or swallowing efficiency and/or reduced* QOL*, irrespective of the stage of the disease.*
Aii. *When patients with PD require treatment for dysphagia, an instrumental assessment of swallowing is indicated to guide the treatment plan.*
Aiii. *Treatment may include optimization of antiparkinsonian treatments, dietary modifications and fluid thickening, strategies for nutritional management, postures, swallowing maneuvers, swallowing exercises, neuromodulation, and medical treatments.*

B) What are the treatment options for dysphagia in PD?

B1) Optimization of PD treatments
Statements are based on core literature consisting of Class II-III-IV level studies [37–41,48–59] *and expert opinion:*

B1i. *Patients should be tested during both the ON- and OFF-state to assess the impact of dopaminergic treatment on swallowing function.*
B1ii. *Dopaminergic treatment should be optimized in patients with PD and dysphagia.*
B1iii. *Patients with PD and dysphagia should preferably consume meals during their best ON-state.*
B1iv. *In patients with PD undergoing DBS, dysphagia should be carefully assessed in the short and long-term to detect changes and provide intervention when necessary.*

B2) Swallowing therapy
Statements are based on core literature consisting of Class I-III-IV level studies [43,63–67,71–75,80,82,86,87,90–93] *and expert opinion:*

B2i. *Standard swallowing therapy is recommended for some patients with PD and dysphagia with sufficient cognitive level to follow clinicians' indications. When standard swallowing therapy is prescribed, it should address specific biomechanical and/or pathophysiological mechanisms, based on the instrumental findings.*
B2ii. *Liquid thickeners may be beneficial in dysphagia associated to PD provided that the viscosity selection is guided instrumentally and the risk of dehydration is monitored.*
B2iii. *Postures may have positive effects on dysphagia in some patients with PD. In the absence of precise selection criteria, based on expert opinion, effect of postures may be suggested on a case-by-case basis.*
B2iv. *Skill-based therapy may be prescribed in non-demented PD patients with dysphagia to increase the precision of muscle contraction during swallowing. When prescribed, it should address specific biomechanical and/or pathophysiological mechanisms, based on the instrumental findings.*
B2v. *LSVT® is designed to treat voice and should not be considered as a primary treatment for dysphagia in patient with PD.*
B2vi. *EMST may be beneficial in some patients with PD and penetration or aspiration and adequate cognition to improve airway protection. When prescribed, it should address specific biomechanical and/or pathophysiological mechanisms, based on the instrumental findings.*

B3) Neuromodulation
Statements are based on core literature consisting of Class I-II-III-IV level studies [57,98–101] *and expert opinion:*

B3i. *There are no data available on the effects of tDCS in patients with PD and dysphagia.*
B3ii. *rTMS may be associated to a beneficial effect on swallowing function in patients with PD, but its use is limited to research settings for the identification of standard protocols of stimulation.*
B3iii. *The use of TES is not recommended for the treatment of dysphagia in patients with PD.*

B4) Medical treatments
Statements are based on core literature consisting of Class IV level studies [102,103,105] *and expert opinion:*

B4i. *BT injection may be an option to treat patients with well-documented UES impairment, in the absence of other significantly impaired swallowing mechanisms or where the UES impairment can be considered as the main pathophysiological mechanism of dysphagia based on instrumental findings.*
B4ii. *BT injection should be electromyography-guided and performed by experienced clinicians to avoid adverse effects.*
B4iii. *There is insufficient evidence on the efficacy of vocal fold augmentation to reduce aspiration risk in patients with PD and dysphagia.*

stimulation of the GPi [48,55], while one study targeted the caudal zona incerta [57]. Another study compared bilateral stimulation in STN with the combined stimulation of STN and substantia nigra [50]. In one study, the stimulation was unilateral [55]. Xie and colleagues analyzed the effects of a low-frequency stimulation (60 Hz) in patients with PD refractory to the standard high-frequency stimulation (130 Hz) [49]. Some studies provided low-level evidence (Class IV) of positive effects for the STN-DBS on dysphagia. Improvements of pharyngeal kinematic and/or patient-reported symptoms during the STN-DBS stimulation were reported in 6 studies [51–54,56,59]. Conversely, there is some evidence (1 Class II study [48] and 1 Class IV study [55]) of long-term potential negative effects on swallowing due to STN-DBS. Six months after surgery, Robertson et al. described detrimental effect of STN DBS on jaw kinematics during the oral preparatory phase, whereas an improvement of jaw kinematics in patients with GPi DBS [52]. An analogous trend on the pharyngeal phase of swallowing was reported by

Troche et al., who found a worsening of the Penetration-aspiration (PAS) [60] score in patients with STN DBS and an improvement of the PAS score in patients with GPi DBS [52]. Thus, if DBS is recommended for the treatment of other motor symptoms, clinicians should carefully monitor changes in swallowing function both in the short and the long-term.

3.3.2. Swallowing therapy

In patients with PD, due to the progressive nature of the disease, swallowing therapy aims to maintain functional swallowing to provide adequate nutrition and hydration without pulmonary complications as long as possible. Swallowing therapy relies on compensatory and rehabilitative strategies. Compensatory strategies are designed to ease the bolus flow by making eating and drinking safer and easier without actually changing the physiology of the swallow [16,61,62]. Rehabilitative approaches have the goal of improving swallowing function by changing swallowing physiology and promoting long-term changes [61,62].

Conventional swallowing therapy includes a variety of interventions, such as counseling on swallowing physiology and dysphagia pathophysiology, strategies for meal management, and behavioral therapy (swallowing maneuvers, strengthening exercises, thermal tactile stimulations). Although widely applied in clinical practice, only 4 studies investigated the efficacy of conventional swallowing therapy in patients with PD [63–67]. Luchesi and colleagues followed-up 24 patients with PD who received swallowing therapy including compensatory strategies, swallowing and non-swallowing exercises, and sensory stimulation every 3 months over a 5-year period [63,64]. Based on the recommended diet type following a fiberoptic endoscopic evaluation of swallowing, they reported improved swallowing function in 10 patients, maintained swallowing function in 5 patients, and a worsening of the swallowing function in 9 patients. Another study analyzed the impact on QOL of a 4-month weekly intervention of conventional swallowing therapy including food modifications and postural adaptations [65]. The study reported a trend for an improvement in all the domains of the SWAL-QOL questionnaire [68], but the lack of a control group and instrumental outcomes limits the strength of the results. Manor and colleagues compared the efficacy of conventional swallowing therapy with the efficacy of a video-assisted swallowing therapy [66]. During the video-assisted swallowing therapy, video-recordings from the fiberoptic endoscopic evaluation of swallowing are showed to the patients to improve patient's knowledge on swallowing physiology and pathophysiology and provide off-line biofeedback during the training of compensatory techniques. Both groups significantly reduced the severity of pharyngeal residue, with significantly higher improvements in the video-assisted group. Moreover, swallowing-related QOL was significantly improved in the video-assisted groups after the treatment and at the 6-months follow-up. Finally, Wei and colleagues investigated the efficacy of a community swallowing management regimen targeting patients with PD and dysphagia and their caregivers and including education training sessions on dysphagia knowledge, strategies for meal management, compensatory strategies, and strengthening exercises [67]. The authors concluded that 68% of the patients improved the swallowing function after the treatment, however the outcomes used are unclear.

Based on the retrieved studies, there is low-level evidence (Class III-IV [63–67]) that standard swallowing therapy can improve dysphagia in PD. When adopted in the early phases of PD, the swallowing therapy seems to be associated with a greater improvement in QOL [65]. However, the definition of conventional swallowing therapy is unclear and/or inconsistently applied in the published literature. The lack of control groups of patients with no intervention reduces the quality of the evidence. Some studies [65,66] excluded patients with dementia. The ability to follow clinician's instruction is critical for many swallowing and non-swallowing exercises, thus, in case of cognitive impairment, the range of interventions from conventional swallowing therapy would be limited.

Compensatory treatments include bolus modifications, postures, swallowing maneuvers, and sensory stimulation. The effects are immediate. However, the long-term effects on dysphagia-related complications may not reflect immediate benefits.

Aspiration of thin liquids is common in PD. In patients with dysphagia, thickening of liquids improves the situation by slowing down the flow of liquids, which allows more time for airway closure [69]. For this reason, liquid thickening is frequently recommended in clinical practice [70]. There is evidence (Class III-IV [43,71–73]) that thickening liquids reduces the risk of aspiration in patients with PD. However, very thickened liquids are often considered unpleasant and a fatigue effect can be observed [71]. Patient-reported palatability was found to be reduced for all types of thickeners, with gum-based thickeners demonstrating lower taste and aroma intensity compared to startch-based thickeners [74]. Conversely, there is no evidence that liquid thickening reduces pneumonia or mortality (Class I [75]) when compared to the chin-down posture intervention with thin liquids. In one study, patients with PD randomized to honey-thickened liquids were reported to exhibit a higher rate of aspiration pneumonia, dehydration, fever, and urinary tract infections compared to patients drinking thin liquids with the chin-down posture, although the differences were not significant and both interventions were associated to a lower than the expected rate of pneumonia [75]. New generations of gum thickeners cause a strong viscosity-dependent therapeutic effect on the safety of the swallow. This effect depends on the phenotype and is similar among elderly, PD and post-stroke patients [73]. It is, however, important to consider that very thickened liquids may be associated to post-swallow pharyngeal residual and dehydration [74,76–78], which may be problematic in some patients with PD.

The chin-down posture is another strategy to reduce aspiration of thin liquids, by promoting airways protection during swallowing [79]. Because of cognitive impairment, anatomic postural changes, and tremor, chin-down posture in patients with PD may be challenging. There is still insufficient evidence (Class III-IV [71–80]) that postures can improve dysphagia in PD. The chin-down posture was reported to successfully eliminate aspiration in 1 out of 3 patients with PD [71]. It should be taken into account that patients with PD often present with abnormal posture, such as camptocormia and antecollis, which results in spontaneously adopting a chin-down posture during swallowing. Hence, when aspiration of liquids and foods is detected in these patients, the possibility to apply a chin-down posture as a compensatory strategy to reduce the aspiration risk is limited.

Thus, the use of compensatory strategies may be suggested in patients with PD on a case-by-case basis. The recommendation should always rely on three aspects: (i) the immediate efficacy to eliminate aspiration verified during the instrumental assessment, (ii) the risk of pulmonary complication and dehydration, and (iii) patients' and caregivers' preferences.

Swallowing exercises from conventional swallowing therapy are designed to improve the strength of the muscles involved during swallowing. Recently, a shift toward including skill-based exercises in the swallowing therapy of PD patients has been observed. Skill training is the process of learning and fine-tuning new sequences of movements [81]. Only one study evaluated the effects of skill training on swallowing in 10 patients with PD [82]. The study included 10 patients with PD and dysphagia. Patients with dementia were excluded. Patients underwent 10 skill training therapy sessions over a 2-week period using a surface EMG biofeedback device and the Biofeedback in Swallowing Skill Training software. The protocol included tasks with increasing difficulty and immediate feedback. The aim was to improve the precision of swallowing muscle contraction by developing conscious control over timing and strength of swallowing. Post-treatment, swallowing rate for liquids, surface EMG durational parameters of premotor time and pre-swallow time improved. Although the short-term results suggest an improvement in swallowing efficiency, there is currently low-level evidence (Class IV) that swallowing skill-based training can improve

dysphagia in PD [82]. Therefore, additional research is needed to better quantify the efficacy of this approach.

Lee Silverman Voice Therapy (LSVT®) is a standardized and intensive voice training designed specifically for patients with PD. LSVT® improved loudness up to two years after treatment [83], as well as speech intelligibility, breath support, and voice quality [84,85]. The possibility to transfer voice and speech effects of LSVT® on swallowing function in patients with PD was investigated by 2 Class IV studies [86,87], which yielded low-level evidence that LSVT® influences swallowing as a by-product of voice treatment. Sharkawi and colleagues investigated swallowing changes on VFSS in 8 patients with PD who underwent the LSVT® [86]. After treatment, they observed a reduction of half of the swallowing motility disorders observed at the baselined and an improvement in some swallowing temporal measures and in oral residue. Miller et al. analyzed the swallowing effects of LSVT® in 20 patients with PD with vocal deterioration and adequate cognition to perform the treatment [87]. PD severity was mild and 40% of the patient sample reported mild symptoms of swallowing impairment. Self-reported swallowing assessment was found to be improved both 1 week and 6 months after the end of the treatment compared to the baseline. Significant changes in pharyngeal constriction, upper esophageal sphincter opening, and residue were detected during VFSS, although VFSS measures were generally normal at baseline. However, LSVT® does not specifically target swallowing function and it should not be considered as a primary treatment of dysphagia in PD.

Expiratory muscle strength training (EMST) is a behavioral treatment aiming to increase expiratory and submental muscle force production. EMST is known to be effective in improving maximum expiratory pressure and cough effectiveness [88,89]. The efficacy of EMST on swallowing function in patients with PD has been investigated by several studies. In 2009, Pitts and colleagues studied 10 mid-stage patients with PD exhibiting penetration or aspiration during videofluoroscopy and adequate cognition who underwent a 4 -week training using the EMST [90]. After training, several parameters of volitional cough were improved and the PAS score was significantly reduced. However, 6 out of 10 patients continued to exhibit penetration after the training. In 2010, Troche et al. conducted a randomized controlled trial on 68 patients with PD reporting symptoms of dysphagia [91]. Patients were randomized to the active EMST and the sham-EMST. After the 4-week training, only the patients in the active EMST showed a significant although small reduction in the PAS score (mean change 0.61 ± 1.43). Afterwards, 10 patients in the active EMST training underwent a detraining period and were reassessed with VFSS after 3 months [92]. After the detraining period, PAS scores were on average unchanged compared to the post-training assessment. However, no data from the control group were available at this time-point. Finally, Byeon studied the efficacy of EMST in 33 patients with PD and dysphagia and reported significant improvement on swallowing function as detected by VFSS after 4 weeks of training [93]. Therefore, there is low-level evidence (3 Class IV studies [90,92,93], 1 Class I study [91]) that EMST can improve dysphagia in PD, although the effect size is small.

3.3.3. Neurostimulation

Neurostimulation techniques include non-invasive brain stimulation (NIBS) and transcutaneous electrical stimulation (TES).

Researchers have investigated the possibility to use NIBS techniques for dysphagia rehabilitation. NIBS is based on the principle of neuroplasticity, defined as changes in neuronal pathways to increase neural functioning via synaptogenesis, reorganization, and network strengthening and suppression [17]. The most commonly used techniques are transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). The literature search failed to retrieved studies assessing the effects of tDCS on swallowing in PD. Thus, future studies are needed to provide evidence for its application in dysphagia management in this population. There is preliminary evidence from 1 study (Class I [94]) that suggests a positive effect of rTMS on dysphagia in PD. Khedr and colleguaes randomized 33 patients with PD and dysphagia to a sham rTMS group and a real rTMS group (2000 pulses; 20 Hz; 90% resting motor threshold; 10 trains of 10 s with 25 s between each train) over the hand area of each motor cortex (5 min between hemispheres) for 10 days (5 days per week) followed by 5 booster sessions every month for 3 months [94]. The authors found an improvement in self-reported dysphagia, hyoid elevation, and pharyngeal transit time only in the real rTMS group, suggesting that rTMS may be effective in improving swallowing function in patients with PD, although no changes were recorded for penetration and aspiration or residue. Since data are available from a single study on a relatively small sample size and standard treatment protocols are lacking, rTMS for the treatment of dysphagia in patients with PD is currently not recommended in clinical practice.

Transcutaneous electrical stimulation (TES) has been introduced in dysphagia treatment as a therapeutic adjunct to standard swallowing therapy [95,96]. TES delivers stimulation to the muscles through surface electrodes. By stimulating the nerve and the motor end plate of the nerve in the muscle fibers, TES promotes a re-training of the functional muscle contraction patterns [97]. Four studies (I class II study [98], 1 class III study [99], 2 class IV studies [100,101]) investigated the efficacy of TES on swallowing function in patients with PD [98–101]. Baijens et al. tested the effects of TES (VitalStim® electrical stimulator) in different electrode positions (above the hyoid bone, below the hyoid bone, and both) on swallowing function in 10 patients with PD and dysphagia [99]. The majority of temporal, spatial, and visuoperceptual VFSS variables were unchanged during TES regardless of the electrode position. The few significant changes to VFSS parameters suggested a potential detrimental effect of TES on dysphagia in patients with PD, especially when the electrodes were placed only below the hyoid bone. Three studies compared the efficacy of the adjunct of TES to standard swallowing therapy to efficacy of the standard swallowing therapy alone [98,100,101]. Dysphagia significantly improved in both groups compared to the baseline assessment, but no significant difference was found between the two interventions. A group of authors from the Netherlands randomized 109 patients with PD to 3 groups of intervention: (i) standard swallowing therapy, (ii) standard swallowing therapy plus motor-level TES, (iii) standard swallowing therapy plus sensory-level TES. After the intervention no statistical differences in FEES and VFS parameters [98] and in swallowing-related QOL [100] were found among the 3 groups. Similar findings were reported by Park and colleagues comparing the standard swallowing therapy to the standard swallowing therapy with the adjunct of TES in 18 patients with PD and dysphagia [101]. Overall, both groups showed an improvement of swallowing function as measured by VFSS. No significant changes were found between the groups, except for a higher improvement in the hyoid displacement in the TES group. Thus, the adjunct of TES does not seem to result in a significant improvement of dysphagia outcomes in PD beyond those attributable to standard swallowing therapy [98,100,101].

3.3.4. Medical treatments

Medical approaches for dysphagia may be indicated for selected pathophysiological impairments, specifically inadequate lower airway protection and upper esophageal sphincter (UES) dysfunction, by means of pharmacological treatments and surgery.

Among pharmacological options, botulinum toxin (BT) may be considered for the treatment of dysphagia due to spasm and/or reduced relaxation of the UES. BT injection is delivered into the cricopharyngeal muscle (main component of the UES), improving UES relaxation during swallowing. Two studies analyzed the efficacy of unilateral BT injection in the cricopharyngeal muscle in PD patients with dysphagia [102,103]. Few and transient adverse effects on swallowing and voice were reported [103]. There is low-level evidence (Class IV studies [102,103]) that BT injection improves dysphagia in PD. Nevertheless, some aspects should be considered. Firstly, when inadequate UES opening is observed

during VFSS or FEES, a careful electromyographic evaluation of the activity of the cricopharyngeal muscle is recommended to ascertain whether inadequate UES relaxation is due to an altered control of the muscle tone or to other causes which require a different intervention. Pharyngeal high-resolution impedance manometry may also guide the identification and selection of candidates for this treatment. Secondly, before BT injection, it is essential to verify that other swallowing mechanisms, such as laryngeal closure, elevation and anterior misplacement, are preserved. This is essential to maintain airways safety, considering that the BT treatment results in both a greater UES relaxation during swallowing and a lower cricopharyngeal muscle resting tone, which may increase the risk of aspiration of gastric contents from the esophagus. Additionally, BT injection into the cricopharyngeal muscle exposes to the risk of diffusion of the toxin to nearby muscles involved in laryngeal and vocal fold motility with potential risk of respiratory and phonation disturbances [103]. Taken together, it is recommended that BT injection should be electromyography-guided and performed by experienced clinicians that should also optimize the injected dose to obtain the desired effect on the UES, while minimizing the risk of adverse effects.

Glottic insufficiency has been reported in around 60% of patients with PD [104]. Injection laryngoplasty is a surgical technique aimed at augmenting and medializing the vocal fold to decrease the glottic insufficiency caused by a variety of medical conditions. One retrospective Class IV study investigated the efficacy of vocal fold augmentation through injection laryngoplasty in adjunct to speech and language therapy on a small sample of patients with PD ($n = 14$) with glottal insufficiency and vocal bowing [105]. The procedure was found to be safe in all patients. The authors reported that injection laryngoplasty seems to improve glottic closure and reduce the severity of patient-reported symptoms of dysphagia. However, no control group was available, the outcomes data were missing for some of the patients, no statistical analysis was performed due to the small sample size, and instrumental assessment before and after treatment was lacking to confirm the efficacy and safety of the procedure on swallowing. Thus, future studies are needed to test the feasibility of injection laryngoplasty as a therapeutic option for dysphagia in PD.

3.4. Nutritional management

3.4.1. Nutritional interventions

Consensus statements on nutritional management of patients with PD and dysphagia are reported in Box 2. Despite limited evidence from intervention studies on the management of dysphagia by oral nutritional interventions is available, there is strong consensus on the importance of nutritional care in PD [44] and it is substantially agreed that referral to a nutrition specialist should be part of the routine clinical workup since the earliest stages of PD [44,45]. Continuous monitoring is also mandatory.

Nutritional interventions for dysphagia in PD should be prescribed on the basis of a multi-disciplinary evaluation by specialized personnel (neurologists, ENT, phoniatricians, gastroenterologists, speech-language pathologists, dieticians, and clinical nutritionists).

Nutritional interventions should address not only the safety and efficacy of swallowing, to reduce the risk of dehydration, malnutrition, and aspiration, but should also take into account general and disease-specific issues. Furthermore, interventions should be balanced on an individual basis with pertinent risk-benefit analysis and monitoring of the impact on QOL.

Dietary counseling including the use of oral nutritional supplements and texture-modified oral diets represents the first-line nutritional strategy for treating dysphagia. To prevent or treat malnutrition and muscle loss, the diet should be of adequate protein-calorie content and density, resulting in higher energy intake with reduced meal interruption and feeding assistance. Nevertheless, monitoring of compliance is mandatory as these diets could be unpleasant and may lead to reduced energy and protein intake [106]. As neutral aminoacids and levodopa compete for transportation through a specific active-transport system in the small intestine and at the blood-brain barrier, protein-redistribution diet (low-protein breakfast and lunch and consumption of a second-course only at dinner) with normal protein content (1.0–1.2 g/kg/day) should be considered to maximize levodopa absorption and efficacy,

Box 2
Statements on the nutritional management of patients with PD and dysphagia.

C) What are the nutritional interventions for patients with PD and dysphagia?
Statements are based on expert opinion:

Ci. *Nutritional intervention should be prescribed based on a multidisciplinary evaluation (including neurologist, ENT, phoniatrician, gastroenterologists, speech-language pathologists, dietitians, and clinical nutritionists) and may include dietary counseling (including oral nutritional supplements), texture modified diet, as well as artificial nutrition.*

Cii. *Intervention should focus not only on safety and efficiency of swallowing, swallowing-related* QOL*, but also on both general (nutritional status, hydration status, energy balance) and disease-specific (levodopa containing medications and protein intake interactions, vitamin status, fiber intake) issues.*

D) When should percutaneous endoscopic gastrostomy indicated for the nutrition of patients with PD and dysphagia?
Statements are based on expert opinion:

Di. *PEG should be placed in case of inadequate oral intake expected to be longer than 4 weeks resulting in involuntary body weight loss (≥5% in 1 month or ≥ 10% in 3 months) and/or significant risk of prandial aspiration exceeding the risk of aspiration of reflux.*

Dii. *In case of potentially reversible swallowing impairment (short-term exacerbation or expectations of positive treatment response), nasogastric tube feeding should be considered.*

Diii. *PEG feeding should be carefully considered on an individual basis taking into account patient and family choice, caregiving context, health ethics, prognosis and* QOL*.*

Div. *In case of dementia, PEG insertion is not indicated.*

Dv. *In case of continuous intra-jejunal levodopa infusion, oral nutrition may be continued in patients with sufficiently safe and efficient swallowing.*

Dvi. *Oral hygiene interventions and oral intake (if safe based on clinical/instrumental assessment) should be continued even after PEG placement.*

particularly in patients experiencing motor fluctuations. There is no evidence supporting the use of low-protein, gluten-free or plant-food based diets. Dietary modifications should also address the need to guarantee or improve the status of relevant vitamins (vitamin D, folic acid, vitamin B12) [44]. The maintenance of adequate fiber intake with texture-modified diets may be difficult and should be also taken into account considering the frequency of constipation in patients with PD [44,107].

3.4.2. Percutaneous endoscopic gastrostomy

There are no PD-specific recommended criteria to guide percutaneous endoscopic gastrostomy (PEG) placement in daily practice and there are no data indicating that tube feeding prolongs survival in PD or improves QOL. Accordingly, we suggest referring to available international guidelines dealing with this issue [108–110]. Tube feeding is not recommended in patients with severe dementia and in the terminal phase of life [108–110].

Where oral feeding is no longer possible, safe or adequate in covering energy and fluids requirements, thus resulting in significant weight loss (e.g. about 5% in 1 month or 10% in 3 months) and/or dehydration, tube feeding should be considered on an individual basis taking into account patient willingness, caregiving context, ethical reasons, respiratory function and the patient's general condition, prognosis and expected outcomes [45,108,109]. In case of potentially reversible swallowing impairment, nasogastric tube feeding should be considered, but when impairment is expected to be longer than 4 weeks PEG insertion should be considered as it has been associated with better QOL [110]. However, PEG placement does not eliminate the risk of aspiration. Accordingly, high-risk patients, as well as those presenting gastroduodenal motility problems, should be candidates for a jejunal extension tube (PEG-J) or jejunostomy and post-pyloric feeding [109]. In the advanced stages of the disease, patients with PD may require continuous intrajejunal delivery of levodopa-carbidopa intestinal gel via a PEG-J. In presence of concomitant dysphagia, anticipated enteral nutrition through the gastric port could be considered in these patients. Patient's monitoring is mandatory as the infusion of nutrition could negatively affect levodopa absorption and efficacy [111,112] and both interventions may need implementation by adjusting medication dosages and/or changing the nutritional treatment regimen. Nonetheless, gastroparesis might be a limiting factor for gastric feeding and the use of prokinetic agents should be considered [45].

Enteral nutrition could be either exclusive or integrative as oral intake should be continued even after PEG placement, if safe based on instrumental assessment. In both cases, oral hygiene interventions should be implemented to reduce the risk of aspiration pneumonia.

3.5. Limitations of the study

Some shortcomings of the present work should be mentioned. Firstly, the recruitment of participants lacked a strictly codified methodology for selection and was mainly based on practical considerations and on their voluntary acceptance of our invitation. Thus, the expert group had a prevalent representation of neurologists compared to other specialists and of Italian specialists compared to specialists from other countries. Consequently, it is possible that the statements elaborated by this panel group do not reflect entirely the point of view of the wider international medical and scientific communities. Nevertheless, it should be mentioned that we put in place several measures to involve as many experts in the field as possible and that, once the panel was created based on voluntary adhesion, the ruling process was supported by a thorough revision of the data available from the literature. Another limitation of the consensus process is that PD patients, their caregivers, or representatives were not involved.

3.6. Directions for future research

This consensus process identified several research gaps emerged on the treatment and the nutritional management of PD patients with dysphagia that could not be properly addressed by the panel of experts due to the lack of reliable evidence. In particular, the experts agreed on the need for large, well-designed studies to:

1. investigate the optimal time in the disease to initiate intervention for swallowing and to explore the impact of the natural evolution of dysphagia in patients with PD
2. evaluate the efficacy and adverse effects of compensatory treatment on clinical endpoints such are nutrition, hydration, respiratory complication, hospital readmission, QOL and mortality in patients with PD and dysphagia
3. compare the efficacy and complications of different swallowing treatments and to evaluate their effect on the progression of dysphagia in PD
4. evaluate the impact of nutritional intervention for dysphagia in patients with PD, including the impact of PEG placement on nutrition, respiratory complication, QOL and mortality.

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Data availability

Data are available in the ZENODO repository, with the following DOI https://doi.org/10.5281/zenodo.5535746.

Appendix 1. Research questions based on PICO

Participants/population

Subjects with Parkinson's disease.

Intervention(s), exposure(s)

Questions on screening and diagnosis: presence and absence of oropharyngeal dysphagia, and any diagnostic test or screening test.

Questions on prognosis: oropharyngeal dysphagia as exposures.

Question on treatment: any treatment of oropharyngeal dysphagia.

Comparator(s)/control

Not applicable.

Main outcome(s)

The primary outcome of the systematic review is to provide the evidence to an International Consensus Conference on oropharyngeal in Parkinson's disease (PD), that has the aim to (1) establish the screening pathway of oropharyngeal dysphagia in PD, (2) define the diagnostic criteria of oropharyngeal dysphagia in PD, (3) define the prognostic value of oropharyngeal dysphagia on MSA survival and QOL, (4) suggest the therapeutic options for oropharyngeal dysphagia.

Appendix 2. Search strategy on MEDLINE

("deglutition disorders"[MeSH] OR ("deglutition disorder"[All Fields] OR "deglutition disorders"[All Fields] OR "swallowing disorders"[All Fields] OR "swallowing disorder"[All Fields] OR ("deglutition disorders"[MeSH Terms] OR ("deglutition"[All Fields] AND

"disorders"[All Fields]) OR "deglutition disorders"[All Fields] OR "dysphagia"[All Fields])))

AND

("Parkinson's disease"[Mesh] OR ("Parkinson's disease"[All Fields] OR "Parkinson's disease"[All Fields] OR Parkinson[All Fields]))

Appendix 3. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2021.120008.

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