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Pill swallowing in Parkinson's disease: A prospective study based on flexible endoscopic evaluation of swallowing

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ABSTRACT

Background: This study evaluates the prevalence, characteristics, and predictors of the difficulty of swallowing medication in Parkinson's disease (PD).
Methods: In this prospective controlled, cross-sectional cohort study, the ability to swallow four different placebos was assessed using flexible endoscopic evaluation of swallowing (FEES) in 118 PD patients and 32 controls. The association between a patient's swallowing ability for each pill and water, patient characteristics and dopaminergic response was examined. The value of two swallowing screening questions was also evaluated.
Results: Substantially impaired ability to swallow pills was found in 28% (n = 33/118) of patients and 16% (n = 5/32) of controls (p = 0.18). Higher disease severity was associated with more problems with swallowing pills (p = 0.03), but PD patients with short disease duration (< 2 years), low H&Y stage (1–2), and younger age (< 70 years) were also affected (each at least in 20%). Capsules were the easiest to swallow while oval tablets were the most difficult (p < 0.01, r = 0.21). Most patients (73%, n = 24/33) presented with swallowing problems only for a single formulation. Aspiration of water was found in 48% of patients, suggesting a possible increased risk of aspiration when taking dissolved tablets. Standardized questionnaires showed insufficient sensitivity (52% both) but fairly good specificity (69–74%) for dysphagia of pills. Dysphagia for medication was not associated with a lack of dopaminergic response.
Conclusions: Dysphagia of medication occurs preferentially in advanced disease stages. An assessment of pill swallowing using FEES is suggested at least in patients reporting swallowing problems. Capsules might be preferentially used when dysphagia is suspected.

1. Introduction

Dysphagia is common in patients with advanced Parkinson's disease (PD), but can occur early in the course of the disease where it is assumed to be underreported and underestimated [1,2]. Several pathophysiological findings are highly prevalent in PD. Repetitive tongue movements (back and forth, referred to as “tongue pumping”) prolong the retention time of pills in the oral cavity, which leads to the risk of premature dissolution. This risk is further increased by impaired tongue base retraction, which promotes pharyngeal residues predominantly in the valleculae. Xerostomia increases oral retention time and impedes esophageal transit [3]. The severity of dysphagia for food and fluids is individually different and depends on the consistency of the nutriment [4]. Caregivers of PD patients with swallowing difficulties frequently modify oral medications. Crushing or splitting tablets or opening capsules might facilitate the administration process, but this practice is associated with an increased risk of medication administration errors [5–7]. Especially in late PD stages, the efficacy of anti-parkinsonian medication is often non-predictable. Usually, this is considered to be related to disease progression [8] and gastrointestinal absorption failure [9]. However, it has been shown recently that on-off fluctuations in PD patients might be related to dysphagia of pills [10]. Pills can get stuck unnoticed in the pharynx or remain in the oral cavity in PD patients with dysphagia [2].

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We suspected that PD patients have a variable ability to swallow different forms and consistencies of tablets and capsules. This might lead to an unequal risk of aspiration and residues with a consecutive lack of efficacy [11].

In the present study, we aimed to assess in an unselected "real-life" PD outpatient cohort the ability of patients to swallow different placebo pills that were comparably shaped to typical anti-parkinsonian medication. We hypothesized that the ability to swallow pills differs among PD patients not only with respect to patient characteristics, such as disease severity or disease duration, but also to the pill characteristics, such as size, form, and surface of the applied pill(s). Furthermore, we assessed for correlation between difficulties with swallowing pills to swallowing water to evaluate whether the frequent recommendation of taking pills with water or dissolving pills in fluid is useful for PD patients with dysphagia. We also evaluated the value of two standard screening questions to assess difficulties in pill swallowing and the association between dysphagia of medication and clinical response to medication.

2. Material and methods

2.1. Study design and subjects

This prospective, controlled, cross-sectional cohort study was conducted at the University Medical Center Hamburg-Eppendorf between March 30 and May 13, 2016. A total of 122 of 146 (84%) consecutive outpatients with a confirmed diagnosis of PD and 32 healthy control subjects without dysphagia consented to participate. Patients belonged to an unselected "real-world" PD cohort undergoing flexible endoscopic evaluation of swallowing (FEES) as the gold standard technique to measure dysphagia independent from subjective dysphagia. We assessed the patients swallowing four differently shaped placebos compared to the usual anti-parkinsonian pills and correlated swallowing ability with patient characteristics, dopaminergic response, and ability to swallow water as medication is usually taken with or is dissolved in fluids. Furthermore, the diagnostic value of two swallowing screening questions was evaluated.

The patient sample and the applied FEES technique have been described in detail in a previous publication [2]. See Table 1 for an overview of the patients' characteristics. Exclusion criteria comprised atypical and secondary Parkinson syndromes, as well as other diseases accompanied by dysphagia. Therefore, all patients underwent a thorough otorhinolaryngological and neurological examination before being included in the study. Four patients had to be excluded: one patient due to soft palate cancer, two patients due to early termination of FEES, and one patient because pill swallowing had to be ended prematurely. Thus, 118 patients were eligible for analysis.

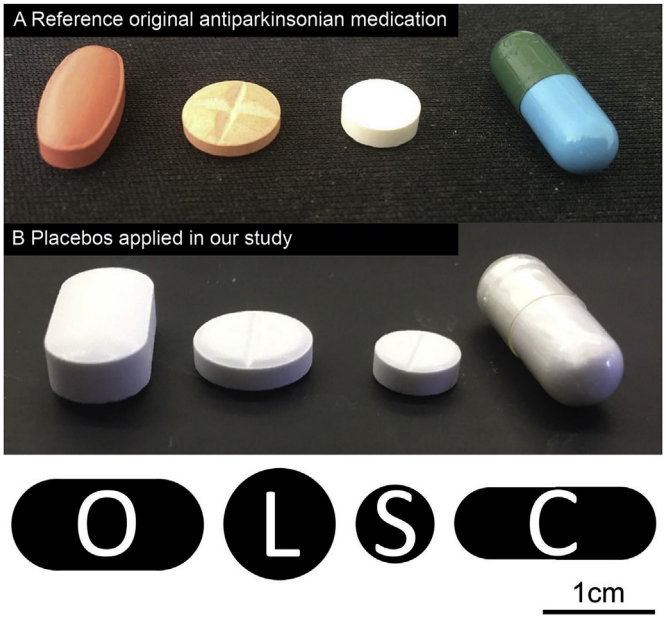

Fig. 1. Shape of oral medication.
O oval tablet (17 mm length), *L* large round tablet (10 mm diameter), *S* small round tablet (7 mm diameter), *C* capsule (18 mm length).

The local ethics committee of the Medical Council Hamburg approved this study (trial number PV5089) and written informed consent was obtained from all participants.

2.2. Assessments

The participants underwent a standardized clinical (otorhinolaryngological and neurological) examination and FEES by otorhinolaryngologists with more than 10 years of experience in FEES. The FEES

Table 1
Subject characteristics of PD patients and controls.

				Oral medication swallowing in PD patients (n = 118)		
	PD patients (n = 118)	p-values	Controls (n = 32)	Not or little impaired (n = 85)	p-values [adj.]	Substantially impaired (n = 33)
Age (years)	69.0 ± 10.1	0.60[a]	68.1 ± 10.7	67.5 ± 10.7	0.02 [0.25][a]	72.7 ± 7.3
Men	79 (67%)	0.14[b]	16 (50%)	54 (64%)	0.28 [1.00][b]	25 (76%)
Disease duration (years)	9.7 ± 7.1	NA	NA	9.1 ± 7.0	0.09 [0.97][a]	11.5 ± 7.3
DBS, n (%)	28 (24%)	NA	NA	19 (22%)	0.63 [1.00][b]	9 (27%)
H&Y stage 1	5 (4%)	NA	NA	5 (6%)	0.26 [1.00][b]	0 (0%)
H&Y stage 2	57 (48%)		NA	44 (52%)		13 (39%)
H&Y stage 3	32 (27%)		NA	20 (24%)		12 (36%)
H&Y stage 4	20 (17%)		NA	14 (16%)		6 (18%)
H&Y stage 5	4 (3%)		NA	2 (2%)		2 (6%)
MDS-UPDRS I-IV	58.7 ± 28.5	NA	NA	53.9 ± 27.0	< 0.01 [0.03*][a]	71.1 ± 29.1
MDS-UPDRS III	31.4 ± 14.5	NA	NA	29.3 ± 13.9	0.01 [0.14][a]	36.8 ± 14.8
MOCA	21.9 ± 4.8	< 0.001[a]	25.3 ± 3.0	22.6 ± 4.3	0.03 [0.28][a]	20.1 ± 5.5
Cognitive deficit	84 (71%)	0.08[b]	17 (53%)	55 (65%)	0.01 [0.14][b]	29 (88%)
LED (mg)	750 ± 420	NA	NA	702 ± 431	0.02 [0.19][a]	873 ± 369
Levodopa Non-Responder	16/116 (14%)	NA	NA	9/83 (11%)	0.23 [1.00][b]	7/33 (21%)

Adj. Adjusted p-values in [..] for multiple testing (11 comparisons), *DBS* deep brain stimulation, *H&Y* Hoehn and Yahr, *LED* levodopa equivalency dose, *MDS-UPDRS* Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale, *NA* not applicable, *MOCA* Montreal Cognitive Assessment (cognitive deficit in case of < 26 points). Values are mean ± SD unless otherwise indicated. Between-group differences were tested with [a] Mann-Whitney test or [b] Fisher's exact test.
*significant and adjusted p-values.

Table 2
FEES-based graduation of ability to swallow oral medication.

Difficulty Rating	Description	Group Assignment
No	No problems swallowing oral medication	Not or little impaired (n = 85)
Mild	Oral medication remains initially in the oral cavity or pharynx but is felt by the patient and cleared spontaneously or by a swallow of water	
Moderate	Oral medication remains in the oral cavity or pharynx and is either not recognized or cleaning is ineffective	Substantially impaired (n = 33)
Severe	Direct or indirect (coughing during or after swallow) signs of aspiration. Oral medication can only be administered with puree or has to be crushed	

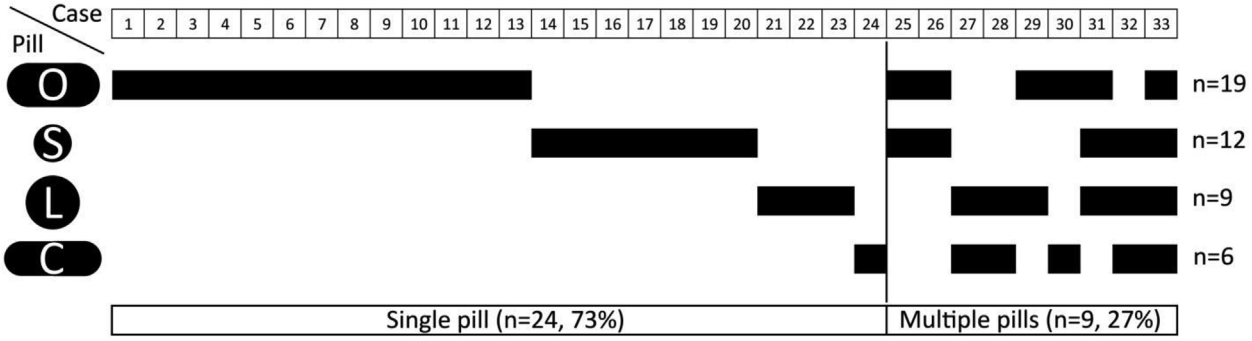

Fig. 2. Shows which pills were involved in PD patients with substantially impaired ability to swallow oral medication.
Shown are the frequencies of involved pills in patients with substantially impaired ability to swallow oral medication. Cases are grouped for single and combined involvement.
O oval tablet, *S* small round tablet, *L* large round tablet, *C* capsule.

exam included requiring participants to drink 90 ml of water quickly through a straw. Penetration and aspiration were assessed using the Rosenbek Penetration-Aspiration Scale (PAS) [12]. Additionally, each participant was administered three different placebo tablets and one capsule (Fig. 1) with a swallow of dyed water in random order. The size, surface, and formulation (i.e., tablets or capsule) of the placebos were compared to four of the most commonly prescribed anti-parkinsonian drugs in Germany [13]. The round tablets had a diameter/volume of 7 mm/0.1 ml and 10 mm/0.2 ml and were manufactured by Winthrop Arzneimittel GmbH. The oval tablet had a length/volume of 17 mm/0.6 ml and was produced by Fagron GmbH & Co. KG. The round and oval tablets had a rough surface (non-coated) and consisted of cellulose, lactose, and magnesium stearate. The capsule consisted of gelatin, had a length/volume of 18 mm/0.8 ml, and was prepared by the pharmacy of our university hospital because no commercially available equivalent could be found.

The ability to swallow the different formulations was evaluated using FEES and was rated on a four-point scale: no difficulties, mild difficulties, moderate difficulties, and severe difficulties (Table 2). Based on the FEES results, we formed two patient groups: (1) no or little impairment and (2) substantially impaired (i.e., at least one pill was rated moderately or severely difficult).

Prior to FEES, participants answered two questions regarding swallowing medications. Question 14 of the Munich Dysphagia Test - Parkinson's disease (MDT-PD) questionnaire [14] asks specifically for “problems swallowing pills” and offers four options: “I disagree,” “I somewhat agree,” “I mostly agree,” or “I strongly agree.” The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) question 2.3 [15] asks about trouble swallowing pills or meals and offers a five-point scale (normal, slight, mild, moderate, severe).

On the day of consultation, clinical global impression (CGI) of the motor response to oral levodopa within the last two weeks was rated as “clearly given” or “unsafe or not given” by the treating movement disorder specialist considering self-reports by the patients, each patient's medical report, and clinical examination. As two patient cases lacked conclusive data (one patient with duodopa pump for > 1 year, one patient with a single short visit), the levodopa response could be assessed in only 116 of the 118 patients.

2.3. Statistical analysis

Statistical analyses were carried out with the statistical software package SPSS, version 23 (IBM, USA). For interval-scaled data, mean values and standard deviations were calculated and tested for significance with the Mann-Whitney test. For nominal- and ordinal-scaled data, frequencies were computed and tested for significance with the Fisher's exact test. All statistical tests were two-tailed. The alpha-level was set to 0.05. Adjustment for multiple testing was applied for the 11 comparisons between PD patients with no/little and substantial impairment of pill swallowing. Inter-pill comparison was done with the Cochran's Q test. One patient swallowed only the small round tablet (early termination because of silent aspiration); therefore, 117 patients (99%) were included in this analysis.

3. Results

Thirty-three of 118 PD patients (28%) showed substantial (moderate or severe) impairment in being able to swallow medication. Common problems included that pills dissolved in the valleculae, piriform sinus or oral cavity. Other problems included coughing and that the patient needed to drink water repeatedly after swallowing the pills. Examples are given in Fig. 1 esupp. The distribution of single and combined medication formulations in PD patients with a substantially impaired ability to swallow medication is given in Fig. 2.

3.1. Association between patient characteristics and difficulty in swallowing oral medication

Table 1 shows the association between patient characteristics and the difficulty in swallowing medication. Adjusting for multiple testing, only the total MDS-UPDRS (I-IV) score was found to show significant differences between patients with no or mild impairment (n = 85) and those with substantially impaired ability to swallow medication

(p = 0.03). This indicates that the severity of PD influences the patient's ability to swallow medication.

However, substantially impaired swallowing of medication also occurs early in the course of the disease, as well as in mildly affected or younger patients. Impairment was found in 4 of 20 (20%) patients with a disease duration under 2 years, in 13 of 62 (21%) patients with Hoehn and Yahr stage ≤ 2, and in 11 of 54 (20%) patients younger than 70 years (minimum 56.3 years).

Five controls (16%) showed a substantially impaired ability to swallow pills. A single tablet caused problems in four cases (oval and small round tablet in one case each, and the large round tablet in two cases) and in one case, two tablets (oval and small round tablet) caused swallowing difficulty. All controls were able to swallow the capsule without difficulties. Based on the FEES results (not or minimally impaired compared with substantially impaired), there was no significant difference between controls and PD patients regarding the ability to swallow oral medication (Fisher's exact test p = 0.18).

3.2. Comparing different medication formulations

In patients with a substantially impaired ability to swallow pills, the oval tablet was involved 19 times, the small round tablet 12 times, the large round tablet 9 times, and the capsule 6 times. In 27% (9/33) of patients, several pills caused problems. Hence, in the majority of cases (73%), only a single oral medication was involved (Fig. 2). The ability to swallow the four medication formulations, assessed on the basis of our FEES-based dichotomous classification (not or mildly vs. substantially impaired) with Cochran's Q test (n = 117), differed significantly (p = 0.01). Comparing the pills pairwise after adjustment for multiple testing (Table 1 esupp), we found a significant difference (p < 0.01) between the oval tablet (most difficult to swallow) and the capsule (easiest to swallow) with a small to medium size effect (r = 0.21; according to Cohen [16]).

3.3. Association between impaired pill swallowing and FEES results for swallowing water

Applying FEES, 45% of PD patients with a substantially impaired ability to swallow pills (n = 15/33) had an uncritical PAS of 1 or 2 for water, whereas 48% (n = 16/33) showed a critical PAS of 6–8, reflecting aspiration (Table 2 esupp). However, 23% (n = 15/66) of PD patients with an uncritical PAS for water (PAS 1–2) showed a substantially impaired ability to swallow pills (moderate or severe on the four-point scale).

3.4. Subjective impairment

The diagnostic value of two screening questions for pill swallowing was evaluated. Even choosing a low cut-off (“I somewhat agree”) for the first question, question number 14 of the MDT-PD questionnaire, we found a low sensitivity of 52% (n = 17/33) and a specificity of 69% in PD patients for a correct self-estimation to have problems with swallowing medication (please see Table 3 esupp for details).

The second question, the MDS-UPDRS question number 2.3, resulted in an equally low sensitivity of 52% (n = 17/33) and a specificity of 74%, despite considering also a low cut-off (slight disturbance). Considering all responses to the MDS-UPDRS question number 2.3, 67% of the patients noticed no problem with chewing and swallowing, 22% reported slight problems, 5% mild problems, 6% moderate problems, and no one indicated severe problems (please see Table 4 esupp for details).

3.5. Association with the dopaminergic response

Fourteen percent (n = 16/118) of PD patients had unsafe or no clinical response to dopaminergic medication within the previous two weeks. We found no significant difference between patients with and without or unsafe dopaminergic response regarding the FEES-proven results of ability to swallow medication (Table 1).

4. Discussion

This prospective, controlled study demonstrates a rather high prevalence in PD patients of FEES-proven problems of swallowing oral medication, especially in patients with an advanced disease stage. However, patients of younger age or earlier in the course of the disease also seem to be affected. Results indicate that capsules are easier to swallow than tablets and that smaller tablets or those that are oval might be unfavorable. Half of the patients who had substantial problems in swallowing medication also showed aspiration of water, suggesting that intake of dispersed tablets has to be recommended with caution. Questionnaire-based self-assessment of difficulties with pill swallowing was found to be not sensitive but was fairly specific for objective dysphagia of medication. No association between dysphagia of medication and response to dopaminergic drugs in PD patients was found.

The data of this study suggest that in advanced PD, apart from fluids and food [2], dysphagia for oral medication is frequently encountered. Therefore, the order of “nil per os except for medications” [17] for dysphagic patients should be considered with caution. On the one hand, caution is necessary also for pills for dysphagic patients; on the other hand, treatment by a speech therapist for swallowing disturbances can often enable the patient to continue to take at least some form of medication orally.

We found that the ability to swallow pills was substantially impaired nearly twice as often in PD patients than in controls. The lack of statistically significant differences is likely related to the low number of controls (n = 32) compared to our substantially larger group of patients (n = 118). However, 16% of the controls also showed substantial impairment in their ability to swallow pills. Age, physiological changes, difficulties overriding the natural instinct to chew solids before swallowing, co-morbidities, and polypharmacy are described as factors contributing to pill swallowing problems, especially in the elderly population [18]. However, age was not correlated with substantially impaired pill swallowing in either the PD patients (Table 1) or controls, and the controls did not suffer from relevant co-morbidities. It is known that many people without swallowing problems for food report dysphagia for solid medications [19]. Thirty-seven percent of the population in a general practice reported swallowing difficulties for solid oral dosage forms on a questionnaire [20]. However, there is a lack of data regarding FEES-proven pill swallowing in the normal population or healthy volunteers. The ability to swallow pills is particularly important in patients with chronic diseases as they need to swallow medication daily.

Our data indicate that even PD patients who are younger, less affected and recently diseased can already suffer from substantial impairment of medication swallowing and not being aware of problems. This matches our earlier results of FEES-proven dysphagia for food and water also in less diseased PD patients [2]. In these patients, the routinely used screening questions failed to sufficiently predict dysphagia for food or drinks [21]. In line with this, we found in the present study that both standard screening questions for pill swallowing (MDT-PD [14] and MDS-UPDRS [15]) are insufficient to predict FEES-proven impairment of pill swallowing in nearly half of the affected patients despite applying low cut-offs.

In PD patients, dysphagia might not only lead to aspiration of medication and concomitantly ingested fluid or food, but also a lack of efficiency of oral medication [2]. Pills stick in the oral cavity or even in the pharynx and patients are often unaware of it (Fig. 1 esupp). This might lead to on-off fluctuations [10]. However, we did not find a relation between pill swallowing problems and lack of dopaminergic response. This might be explained by insufficient statistical power due to

the low number of patients without drug response. Another reason might be confounding by the rather global assessment of response to medication by global clinical impression (GCI). The main reason might be that the unsafe or insufficient dopaminergic response found in 14% of patients in this study is related to gastrointestinal absorption problems [9] and/or interaction with meals including proteins [22] rather than to dysphagia. To improve intestinal absorption and accelerate the gastric phase, patients are often advised to disperse levodopa tablets or to use soluble levodopa. According to our clinical experience, this is also often suggested to PD patients who report problems with swallowing pills. With the aim of being able to swallow the pills better, dysphagic PD patients or their caregivers often crush the tablets and open the capsules [18]. However, according to the presented FEES findings, almost half of the patients with substantial impairment in pill swallowing also showed aspiration of water. Especially in these patients, dispersion of tablets appears risky. Even a careful and questionnaire-based history of aspiration signs before suggesting that patients take levodopa in dissolved form is not a reliable method and is unsafe for predicting aspiration [2].

In cases with problems in swallowing, pills should be taken rather with protein-free smooth food such as apple puree or with a special medication lubricant [23].

Interestingly, there is a lack of data in the literature regarding the “perfect pill form” to swallow, which likely is related to the lack of FEES-proven pill swallowing studies in general.

We chose placebos that were comparable in size, form, and surface to the usual anti-parkinsonian medication that is prescribed in Germany (Fig. 1). Mostly, the oval tablet (58%) but also the other pills (42%) were difficult for the PD patients to swallow, indicating that there is no specific pill formulation that reliably signals dysphagia. Amongst the tested tablets, the large round form showed a marked trend to be swallowed easiest and might preferably be suggested to PD patients when tablets instead of capsules have to be given.

Our data do not allow brand-specific statements because we did not test placebos of the original producer with identical characteristics of the pills. The oval placebo tablet was not film-coated as the imitated verum tablet is, because a film-coated placebo comparable in size and shape was not available. Because the large capsule was swallowed the best and the large oval tablet the worst, size might play a lesser role than does the surface for swallowing.

In almost three-quarters of patients with a substantially impaired ability to swallow pills, only a single pill formulation caused problems. An individual's ability to swallow a certain pill formulation was not predictable. One patient even struggled with three of the four tablets, all except for the most difficult oval tablet. Another patient struggled exclusively with the capsule (overall actually the easiest to swallow).

Overall, we suggest applying FEES liberally in cases of self-reported general dysphagia, uncertain ability to swallow medication, or questionable efficacy of medication. Based on the FEES-results, the patient can then receive a suitable therapy by a speech therapist, including behavioral treatment, food modification, and other strategies.

Evaluating different medication forms during FEES requires little effort in terms of time and costs but might be clinically relevant for the patient. We suggest as a first step to test the patient swallowing the individually used original pill(s) and, if dysphagia is confirmed, to let the patient try different maneuvers to help them swallow the pills correctly. As the next step to finding suitable therapeutic alternatives with identical active ingredients, we suggest testing several different placebo forms and sizes. Improvement of drug-swallowing then might be achieved by changing the manufacturer or using another pill potency with a different shape and adjusting the frequency of consumption. Furthermore, it could be helpful to consult a pharmacologist with professional knowledge of adapting medication consistencies without changing the pharmacological effects.

In cases where FEES is not available with respect to limited time resources or cost-effectiveness, it appears to be reasonable to begin therapy with a capsule in patients with potential swallowing problems. However, capsules might be absorbed more unpredictably than tablets due to delayed intestinal dissolution resulting in less or delayed efficiency. Data referring to this are still lacking.

Almost half of the patients with a substantially impaired ability to swallow a pill had no relevant problems with swallowing water (PAS 1–2). Therefore, dissolving tablets in water seems to be a suitable option on first sight. On the other hand, a comparable proportion of patients showed aspiration of water (PAS 6–8). Dissolving tablets or using in Germany the popular soluble levodopa formulation in these patients would increase not only the risk for lack of efficiency but also for aspiration pneumonia. Noteworthy is that water swallowing was tested using 90 ml. It has to be further evaluated whether the proportion of patients with water aspiration might be smaller if less water was used. This is clinically relevant because many patients take their medication with only one sip of water, which might be less problematic in terms of aspiration. It also has to be kept in mind that our FEES results indicate that there is a proportion of about 20% of patients with no problems in swallowing water but substantially impaired swallowing of pills that likely would benefit from soluble medication formulations.

In conclusion, problems with swallowing medication are frequent in PD patients, and an advanced disease stage constitutes the major risk factor. Testing pill swallowing should form part of any FEES and especially should be performed in PD patients who report swallowing problems and those patients with insufficient clinical response to oral medication. When FEES is not available and pill swallowing problems are suspected, capsules might be preferentially used.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.02.002.

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