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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms

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Abstract
Purpose We assessed the prevalence of difficulties in swallowing solid oral dosage forms in a general practice population. Reasons, nature, and characteristics of tablets and capsules causing such difficulties were investigated as well as general practitioners' (GP) awareness of these difficulties.
Methods A questionnaire survey was conducted in 11 general practices and consecutive patients taking at least one solid oral dosage form for ≥4 weeks were invited to respond to a questionnaire at the practices and one at home. Physicians completed a short questionnaire for each included patient.
Results Of all participants (N=1,051), 37.4 % reported having had difficulties in swallowing tablets and capsules. The majority (70.4 %) of these patients was not identified by their GP. The occurrence of swallowing difficulties was related to gender (f>m), age (young>old), dysphagia [adjusted odds ratio (adOR): 7.9; $p<0.0001$] and mental illness (adOR: 1.8; $p<0.05$). By asking "Do you choke while eating or drinking?", affected patients could be identified with a sensitivity of 62.6 % and a specificity of 78.1 %. Because of these difficulties, 58.8 % of the affected patients had already modified their drugs in a way that may alter safety and efficacy and 9.4 % indicated to be non-adherent.
Conclusions One in 11 primary care patients had frequent difficulties in swallowing tablets and capsules while GPs grossly underestimated these problems. Therefore, physicians should rule out swallowing difficulties regularly to avoid non-adherence and inappropriate drug modifications. Special attention should be paid to specific patient groups (e.g. women and patients with dysphagia, dysphagia indicators, or mental illness).

Keywords Swallowing difficulties · Dysphagia · Tablets · Capsules · General practitioners · Drug modifications

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Introduction

Each year more than 600 million medication packages are prescribed just to statutorily insured patients in Germany [1]. The vast majority (65 % to 70 %) of all medicines are solid oral dosage forms [2] such as tablets and capsules of different sizes and shapes. Solid oral dosage forms prevail because their manufacturing is generally less complex and thus cheaper than the development of most other pharmaceutical formulations [3]. Moreover, stability problems are rare, a variety of non-toxic excipients is available, and masking of taste is accomplished more easily than for liquids [3] or orodispersible tablets [4]. In addition, tablets and capsules lack relevant drawbacks of liquids; accurate dosing is easier [5] as are handling and dispensing [3]. However, given all these advantages of tablets and capsules, one major point is often not considered: The most important

requirement for adequate efficacy of solid oral dosage forms is the ability to swallow them. Only when taken and delivered appropriately to the site of dissolution, can tablets or capsules unfold their full therapeutic effects [6].

It is well known that children and adolescents often struggle with swallowing tablets and capsules [7]. One possible reason might be the smaller dimensions of the puerile pharynx and the developing oropharyngeal musculature [8]. The lack of experience in swallowing drugs may be a further reason because it was shown that proper swallowing can be successfully trained in children [7, 9]. But not only young people have difficulties swallowing tablets and capsules. Generally, the prevalence of swallowing impairment increases with old age as functional impairment evolves [10, 11] and the number of diseases linked to dysphagia like stroke, Parkinson's and Alzheimer's disease [12], or cancer [13] increase. Up to 35 % of ambulatory patients aged 50 to 79 years [14] and 68 % of nursing home residents have symptoms of dysphagia [15]. Another study revealed that 22 % of patients in nursing homes have problems in swallowing solid oral dosage forms [16]. In a Norwegian general practice population covering all age groups, 26 % of the patients and 40 % of the respondents to an American internet survey reported difficulties in swallowing solid oral dosage forms [17, 18] suggesting that swallowing them is challenging for a large proportion of ambulatory patients.

A major concern in this context is that affected patients [19, 20] or their nursing staff are tempted to modify drugs to ease swallowing [21, 22]. Dosage form modifications, if not specified in the label, will result in an unlicensed use [23] and may limit effectiveness and cause harm to the patient at worst [24]. In such cases the liability lies with the person administering the drug and not with the pharmaceutical company [23].

Both the Norwegian and the American study have several limitations such as a low response rate or selection bias due to the design and conduct of the surveys. Furthermore, the results differ largely and major points of interest, such as frequency, severity, and underlying causes of the difficulties, remain unclear.

In order to clarify those unresolved issues and to assess the general practitioners' (GPs) awareness of affected patients, we conducted a study investigating the difficulties in swallowing solid oral dosage forms in a general practice population. Thus, this study aimed at quantifying the overall prevalence of problems with swallowing tablets and capsules ever experienced by adult patients as well as the prevalence of swallowing difficulties patients actually encountered with their current medication at the time of the survey. Using a structured questionnaire the clinical relevance of difficulties in swallowing was evaluated. Therefore, reasons and nature of swallowing problems were assessed and characteristics of tablets and capsules causing such difficulties were quantified. Moreover, the study aimed at finding out how GPs dealt with such issues to eventually indicate ways for improvement.

Methods

Study population and setting

After obtaining approval by the Ethics Committee of the Medical Faculty of the University of Heidelberg we conducted a questionnaire survey from November 2010 to February 2011 in general practices in Baden-Württemberg, Germany (German clinical trials register number: DRKS00000607). Sixteen GPs in 11 general practices took part in the study. The data collection period in each practice was 1 week. Consecutive adult patients taking at least one solid oral dosage form for at least 4 weeks were invited to take part in the study by the study coordinator; no other inclusion or exclusion criteria were applied.

Structure of the questionnaire

A questionnaire with 32 questions was developed; all participants were asked 24 questions and, if swallowing difficulties were mentioned, eight additional questions were asked. The questionnaire consisted of five major topics. The first one covered demographics, the patient's general condition, and any problems with swallowing tablets and capsules (eight questions). The second topic assessed medication intake habits (six questions) such as posture of the head while swallowing, amount of food or fluid used for medication intake, and deliberate dosage form modifications to facilitate swallowing. The third part (five questions) concentrated on the presence of diseases (e.g. stomatitis or stroke) that may cause dysphagia and problems with swallowing solid oral dosage forms. A fourth section (four questions) assessed the patient's attitude towards medication intake and the knowledge about hazards of dosage form modifications. Patients expressing difficulties were asked to answer eight further questions concerning the kind and burden of difficulties, possible reasons, and how they dealt with these difficulties (e.g. skipping doses).

In a separate questionnaire (medication list) patients had to list all prescription and OTC (over-the-counter) tablets and capsules they took at the time of the survey. For each drug, they were also asked to note the PZN ("Pharmazentralnummer", a unique identification key for all pharmaceuticals in Germany) that allows unequivocal identification of the package size and content and thus provides the most comprehensive information on the

administered drug [25]. Finally, patients were asked to specify for each drug whether it caused any difficulties in swallowing.

In an additional questionnaire the GPs had to evaluate for each of their participating patients whether they expected the patient to have swallowing difficulties and to rate the severity of impairment.

Conduct of the survey

After having given written informed consent the patients were asked the questions of the structured questionnaire in a personal interview that was conducted by the study coordinator at the general practices. In addition, they were asked to fill in the medication list at home and return it to the study center using an enclosed pre-addressed and stamped envelope. To improve the response rate, 3×150 EUR were raffled among all responders and follow-up was carefully planned [26]. Patients not responding within 2 weeks were sent a reminder letter by mail. Patients still not answering within 4 weeks were sent a further letter including an empty copy of the medication list. In order to determine the response rate to the questionnaire and non-responder characteristics like age, gender, and number of solid oral dosage forms of each patient who rejected participation were listed. The response rate was calculated as the percentage of participating patients of all invited patients. The response rate of the medication list was calculated as the number of returned medication lists expressed as the percentage of completed main questionnaires.

The GPs filled in the additional questionnaires on a daily basis and returned them to the study coordinator on the following day.

Data analysis

All main and short questionnaires were entered and double-checked for two-person integrity; disparities of the electronic data were corrected on the basis of the original questionnaires. All solid oral dosage forms were matched via their PZN (used as an identifier) to a drug database that contains all pharmaceuticals of the German market (MMI Medizinische Medien GmbH, Neu-Isenburg, Germany). This enabled checking for concordance of listed and marketed brand name. PZNs revealing slight discrepancies between the brand name in the database and the brand name mentioned by the patients (e.g. due to a spelling error or missing strength or name affix such as –plus) were still accepted as correct. The basis for this decision was that PZNs differ in at least two of their seven digits and are not hierarchically structured. Therefore, it was unlikely that a single spelling error in a PZN causes a match with another drug with a similar brand name and the same active ingredient. Whenever the PZN was incorrect or not stated the brand name and strength of the drug were used to identify the respective PZN; if incomplete or equivocal the drug was excluded from the analysis.

The association of medication characteristics (width, height, length, and diameter) with difficulties in swallowing was then analyzed. Information on the dimensions of the drugs was extracted from the database or obtained from the marketing authorization holder.

Statistical analysis

Our primary endpoint was the proportion of primary care patients having difficulties in swallowing drugs (as mentioned in the main questionnaire). Based on previous surveys [17, 18] difficulties in swallowing were expected in 26 % to 40 % of the patients. Hence, to determine the rate of swallowing difficulties with a desired accuracy of at least 3 % 1,025 patients would be needed (calculated with nQuery Advisor 6.01; Statistical Solutions, Saugus MA, USA).

Patient characteristics are presented as percentages or means ± standard deviation. Metrical data were compared using two-sided *t*-test and categorical data using χ^2-test. The association between difficulties in swallowing solid drugs and diseases linked to dysphagia or dysphagia indicators were evaluated using logistic regression. The corresponding odds ratios (ORs) and the adjusted ORs (adORs) are presented with 95 % confidence intervals (CIs). Additionally, sensitivity, specificity, positive and negative predictive values were calculated. A possible correlation between swallowing difficulties and a general aversion to take drugs was assessed using Spearman correlation. Statistical analysis was conducted with SAS statistical software package, version 9.2 (SAS institute Inc., Cary, NC, USA). A p-value <0.05 was considered significant.

Results

Participants and response rates

Of 1,132 patients invited to participate in this study, 1,051 completed the questionnaire resulting in a response rate of 92.8 % (Table 1). All 1,051 completed questionnaires were included in the data analysis. The medication lists were returned by 912 (86.8 %) of the 1,051 patients (Table 1) and contained 3,480 drugs. Manual identification of PZN was impossible for 118 drugs (3.4 %) because brand name and strength were equivocal or incomplete. These were excluded from the analysis as were orodispersible tablets, liquids, and 122 additional drugs with non-oral routes of administration (e.g. inhaled sprays, eye and ear drops, or

Table 1 Demographic data

	Main questionnaire (n=1,051)	Medication list (n=914)	Non-responders (n=81)
Female gender	55.9 %	54.8 %	66.7 %
Mean age (years)	61.8±15.6	62.7±15.1	62.9±17.0
Mean number of drugs	3.4±2.5	3.8±2.7	3.2±2.1

ointments). Moreover, 18 medication lists (containing 106 drugs) were excluded because of plausibility problems. For instance, medication lists were considered as implausible when patients stated always to have problems with each drug mentioned on the list, but did not report any swallowing difficulties in the main questionnaire. Thus, altogether 3,134 tablets and capsules (90.1 % of all mentioned drugs) were included in the analysis.

Prevalence and burden of swallowing difficulties

In the structured interview, 37.4 % (N=393) of the participants reported having already had problems with swallowing solid drugs at some time; females and younger patients were affected significantly more often (Fig. 1). Actually, 27.2 % (240) of all patients who returned a completed and plausible medication list also had swallowing difficulties with their current tablets and capsules.

Of the affected patients (N=393), 24.2 % experienced such difficulties always, daily, or often, 28.0 % sometimes; and 47.8 % rarely. More than one third (39.4 %) of all patients experiencing such difficulties classified their problems as very severe or severe, 48.1 % as not particularly severe, and only 12.5 % as not severe at all.

Swallowing difficulties were described as drugs getting stuck in the throat, an uncomfortable feeling, the need of repeated swallowing attempts, gagging, choking, coughing while swallowing, or vomiting (Fig. 2). This led 28.2 % of the affected patients to be afraid of taking tablets and capsules and 8.7 % had already feared to suffocate while swallowing tablets or capsules.

Causes for swallowing difficulties

As reasons for swallowing difficulties, 21.1 % of the participants mentioned their aversion to drug intake, a further 19.6 % explained their problems with previous bad experiences. A small proportion (2.8 %) thought their problems arose from difficulties they also had with food. Of all patients who were afraid of taking tablets and capsules, 31.5 % considered their anxiety a reason for their swallowing problems. Patients who mentioned aversion to drug intake as a reason for their difficulties also reported anxiety (28.9 %) and poor palatability (38.6 %) as additional causes; 9.3 % mentioned both.

Reasons given for difficulties related to the dosage form were size (74.6 %), surface (70.5 %), shape (43.5 %), and flavor (22.1 %). Of all tablets and capsules in the medication lists, 5.0 % caused swallowing difficulties always or often

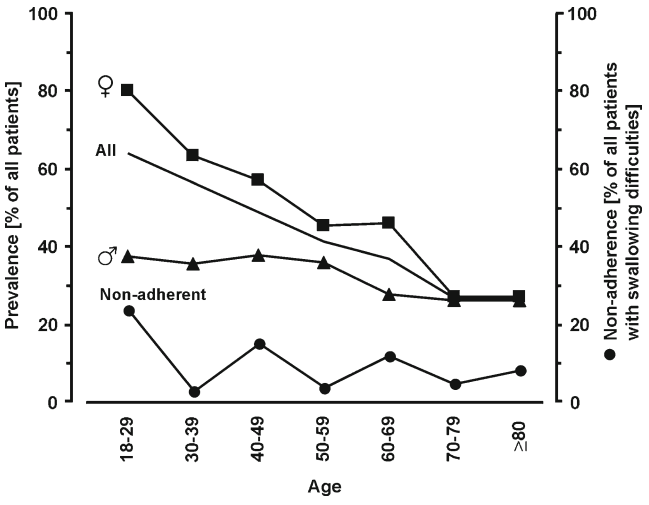

Fig. 1 Prevalence of swallowing difficulties in a general practice population of 1,051 consecutive patients according to age and gender. Women (χ^2-test) and younger patients (t-test) were more often affected (p<0.0001). Proportion of non-adherence due to swallowing difficulties in the affected population of the survey (N=393) according to age

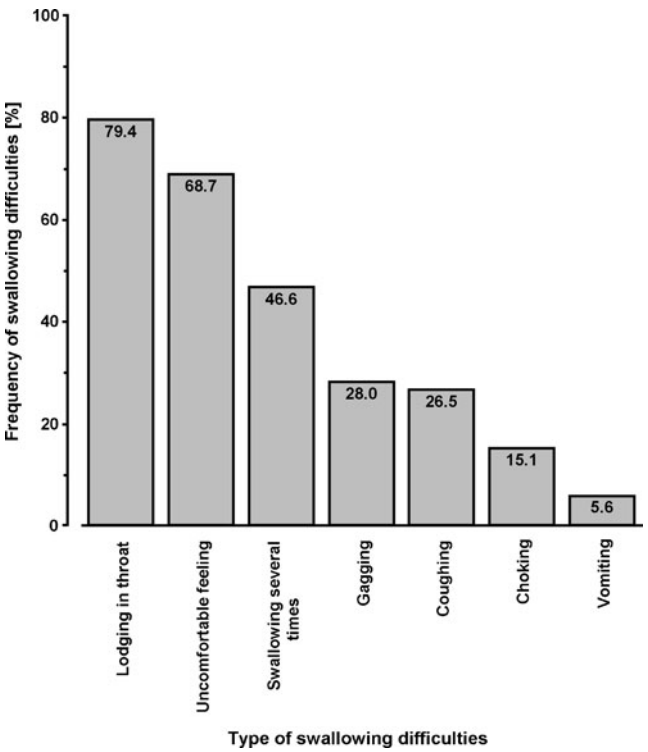

Fig. 2 Frequency and nature of swallowing difficulties in the affected population (37.4 %) of 1,051 consecutive general practice patients

and 11.2 % sometimes. Hard gelatin capsules, soft gelatin capsules and oblong tablets caused problems almost twice as often as tablets with irregular shapes, nearly 1.6 times more frequently than round tablets, and about 1.2 times more often than oval tablets (Fig. 3). The average dimensions of dosage forms that caused swallowing difficulties are shown in Table 2. Difficulties in swallowing tablets and capsules were associated with most of the included diseases known to cause dysphagia and with indicators for presbyphagia or dysphagia such as mouth dryness, choking, coughing, and globus sensation. The corresponding ORs and adORs are presented in Table 3. Conversely, the absence of diseases likely to cause dysphagia appeared to protect from difficulties in swallowing (OR 0.6; CI 0.5, 0.8, $p<0.001$). Patients who are at risk for swallowing difficulties could be identified with a sensitivity of 62.6 % and a specificity of 78.1 % by asking whether they choke while eating or drinking. The sensitivity was increased by asking an additional question such as whether patients cough (sensitivity 72.8 %, specificity 71.7 %) or experience a globus sensation (sensitivity 68.4 %, specificity 76.4 %). The corresponding positive and negative predictive values are presented in Fig. 4. The aversion to medications was weakly correlated with swallowing difficulties ($r^2=0.3$; $p<0.0001$).

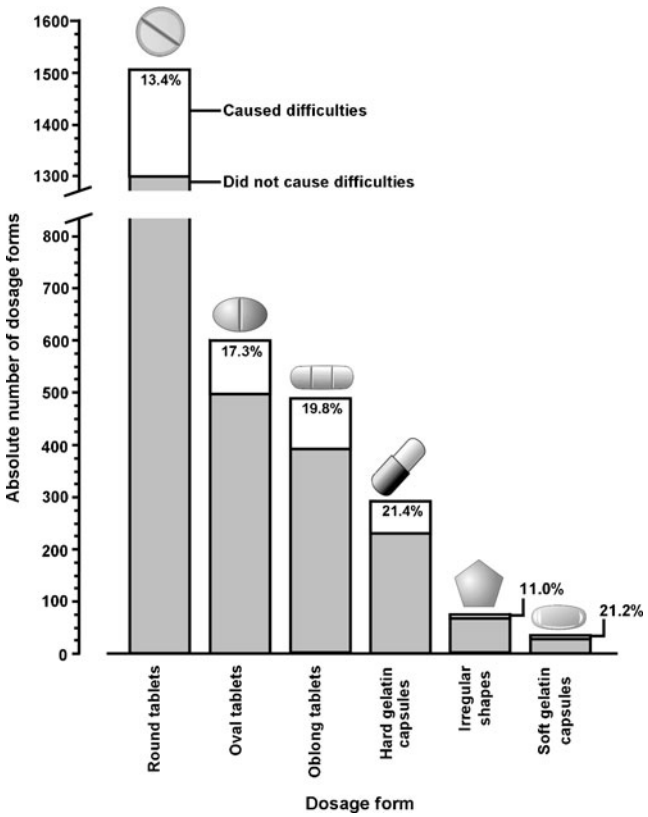

Fig. 3 Proportion of different kinds of tablets and capsules that caused swallowing difficulties in a general practice population of 1,051 consecutive patients

Affected patients (median 3, IQR 4) and females (median 2, IQR 4) had a stronger aversion to drugs than non-affected patients (median 0, IQR 3) and males (median 0, IQR 3).

Administration habits

Regarding administration habits, about two fifths of all respondents reported that they take their tablets and capsules with less than 125 ml fluid, which is less than usually recommended in summaries of product characteristics and package leaflets. A significant proportion (23.2 %) of patients used to take them just with one gulp of water and 1.1 % without any fluid or food. Patients reporting swallowing difficulties used larger amounts of liquids (Fig. 5), ingested their tablets and capsules 2.4 times more often with food, and only 21.1 % swallowed more than one solid oral dosage form at a time. The number of participants who swallowed drugs simultaneously depended on the frequency of swallowing difficulties. Only 4.6 % of patients who reported to have swallowing problems always, daily, or often took more than one solid oral dosage form at a time. In contrast, 16.5 % of patients who were affected sometimes or rarely did so. Concerning the posture of the head, non-affected patients reported significantly more often to swallow tablets and capsules with their head in an upright position (52.4 %) than affected patients 42.4 % ($p<0.01$) whereas affected patients stated more often reclining their head (53.8 %) than non-affected patients (45.8 %, $p<0.01$). Only 2.6 % of all respondents tilted their head forward to swallow capsules and did so with every other solid oral dosage form. Just one person reported to change the head position depending on the dosage form.

The majority (66.0 %) of non-affected patients had no preference for any particular dosage form (tablets or capsules) and 69.7 % did not care about tablet shape while many patients with swallowing difficulties preferred to take round tablets (34.1 %) (Fig. 6).

Dosage form modifications by the patients

Regarding dosage form modifications, 58.8 % of the affected patients had already modified their medication at some time in order to facilitate swallowing; 22.1 % stated to do so always or often (Fig. 7). For instance, modifications included the splitting or crushing of tablets and opening of capsules to get smaller pieces of the dosage form as well as mixing them with food or dissolving them in water (Fig. 8). Women and patients with a general aversion to drug intake modified tablets and capsules significantly more often. Patients who considered their difficulties as very severe and severe modified their drugs in 78.0 % and 74.6 %, respectively. In addition, 50.5 % who considered their problems as not particularly severe, and even 35.4 %

Table 2 Relationship between dimensions of tablets and capsules and swallowing difficulties

	Mean of tablets and capsules that caused difficulties	Mean of tablets and capsules that did not cause difficulties	Difference of the geometric means [%]	*p*-value
Round: Diameter [mm]	8.7±2.0	8.1±1.7	- 7.1	<0.0001
Round: Height [mm]	3.8±1.2	3.5±1.1	- 6.9	<0.01
Oval: Length [mm]	15.0±4.4	13.2±3.3	- 10.3	<0.001
Oval: Width [mm]	7.4±1.8	6.6±1.4	- 9.3	<0.001
Oval: Height [mm]	4.5±1.5	4.6±1.3	+ 3.3	n.s.
Oblong: Length [mm]	16.7±4.0	13.3±4.7	- 22.2	<0.0001
Oblong: Width [mm]	7.3±1.6	6.2±2.0	- 16.3	<0.0001
Oblong: Height [mm]	5.8±1.6	4.9±1.7	- 18.6	<0.01
Irregular shapes: Diameter [mm]	9.4±1.1	8.8±1.4	- 6.7	n.s.
Irregular shapes: Height [mm]	3.5±0.8	3.5±0.8	- 1.2	n.s.
Irregular shapes: Length [mm]	7.3±0.5	8.1±1.5	+ 10.2	n.s.
Irregular shapes: Width [mm]	6.7±0.2	7.0±1.3	+ 2.1	n.s.
Hard capsules: Diameter [mm]	6.8±1.4	6.4±1.2	- 7.1	<0.05
Hard capsules: Length [mm]	19.0±2.0	17.5±2.8	- 9.3	<0.001
Soft capsules: Diameter [mm]	8.6±1.7	8.0±1.1	- 7.0	n.s.
Soft capsules: Length [mm]	20.8±2.0	18.3±5.8	- 16.7	n.s.

who stated being completely comfortable with their difficulties, modified anyway. Half of the modifiers (49.4 %) did not know that such changes of dosage forms may not be allowed and can cause severe health problems. Although older people and patients with a lower level of education knew less about these consequences, educational level was not associated with modification frequency [the levels of education were distributed as follows: general-education secondary school (years 5 to 9) 57.5 %, secondary education (years 5 to 10) 24.0 %, A levels 6.5 %, university 11.1 %, other 1.0 %]. Despite being aware of the possible consequences 32.0 % of the participants modified their medication anyway. Importantly, 9.4 % of the affected patients indicated to be non-adherent due to their swallowing difficulties. The proportion according to age is shown in Fig. 1.

GPs awareness of patients with swallowing difficulties

The GPs' awareness of patients' swallowing difficulties was assessed with short questionnaires which were returned for 1,046 patients. Five patients did not give their full name; therefore, the GPs were not able to answer the questions. The majority of the patients (70.4 %) who expressed swallowing difficulties were not identified by their general practitioner. The proportion of difficulties that was not diagnosed by GPs was lower in patients who had such problems always, daily, or often (59.1 %) than in those who experienced these difficulties only sometimes or rarely (74.0 % not diagnosed). Similar results were found for severity of swallowing difficulties. Generally, women with swallowing problems were identified significantly more often than men ($p < 0.05$). Causes of swallowing difficulties suggested by the participating GPs were neurological disorders, mental illness as well as gastrointestinal diseases or diseases of the neck area.

Altogether, only 6.7 % of all patients (70/1,051) had ever been asked about such problems by their doctor and 4.1 % (43/1,051) by their pharmacist. Conversely, only few of the affected patients (13.7 %) informed their doctor about these problems. Reasons given for this were shame and the preconception that the GPs would not be able to help anyway. Even when being informed, the GPs had changed prescription or advised patients how to facilitate drug administration in only 64.8 % of the cases (Table 4). Of the 470 drugs listed in the MMI database that actually caused swallowing difficulties 16.4 % could have been switched to equivalent non solid oral dosage forms (e.g. liquid therapeutics or effervescent tablets). This proportion might have been higher if switches to therapeutic equivalents or drugs with other strengths would have been considered. Additionally, in 12.3 % of the cases capsules could have been switched to tablets or vice versa if a patient preferred either of these dosage forms.

Discussion

In an unselected German general practice population a remarkably high prevalence (37.4 %) of difficulties in swallowing solid oral dosage forms was found. Indeed, one in 11 patients expressed frequent problems and many of them modified their medication. Nearly one in ten affected patients were non-adherent due to such

Table 3 Risk factors for difficulties in swallowing tablets and capsules

	Non-adjusted[a] ORs[b]			Model A[c]			Model B[d]		
	ORs	CI	*p*-value	adORs[e]	CI	*p*-value	adORs	CI	*p*-value
Diseases linked to swallowing dysfunction									
Dysphagia	14.8	4.4–49.4	<0.0001	5.7	1.6–20.9	<0.01	7.9	3.2–20.0	<0.0001
Stomatitis	2.6	1.6–4.2	<0.001	–	–	–	–	–	–
Diseases of the esophagus	2.2	1.2–4.1	<0.05	–	–	–	–	–	–
Tumors in the neck area	1.9	0.7–5.0	n.s.	–	–	–	–	–	–
Thyroid disorders	1.3	1.3–1.7	n.s.	–	–	–	–	–	–
Dementia	1.1	0.2–6.7	n.s.	–	–	–	–	–	–
Stroke (occurrence of stroke: median 3 yrs[f] (range: 2 mo[g] to 30 yrs)	1.0	0.6–1.7	n.s.	–	–	–	–	–	–
Parkinson's disease	0.4	0.0–3.7	n.s.	–	–	–	–	–	–
Mental illness	1.7	1.2–2.3	<0.01	–	–	–	1.8	1.1–3.0	<0.05
Female gender	1.7	1.3–2.2	<0.0001	1.5	1.1–2.0		1.9	1.2–3.2	<0.01
Age per 10 yrs	0.7	0.7–0.8	<0.0001	0.7	0.7–0.8		–	–	–
Indicators for presbyphagia and dysphagia									
Globus sensation while eating	8.9	4.7–16.9	<0.0001	–	–	–	11.3	3.4–37.6	<0.0001
Coughing while eating	5.4	3.6–8.2	<0.0001	4.4	1.8–10.6	<0.01	–	–	–
Choking while eating	4.4	3.0–6.5	<0.0001	3.3	1.3–8.2	0.01	–	–	–
Xerostomia	2.6	2.0–3.4	<0.0001	3.0	2.0–4.3	<0.0001	2.0	1.2–3.4	–

[a] Non-adjusted ORs: Frequency of dysphagia indicators as covariates dichotomized into "frequent" (always, often, or sometimes) versus "less frequent" (rarely or never). All other diseases are dichotomous (yes/no)

[b] OR: odds ratio

[c] Model A: Frequency of swallowing difficulties as dependent variable dichotomized into "yes" (always, daily, often, sometimes, or rarely) versus "no" (never). Frequency of dysphagia indicators as covariates dichotomized into "frequent" (always, often, or sometimes) versus "less frequent" (rarely or never). All other diseases are dichotomous (yes/no)

[d] Model B: Frequency of swallowing difficulties as dependent variable dichotomized into "very frequent" (always, daily, or often) versus "less frequent" (sometimes or never). Frequency of dysphagia indicators as covariates dichotomized into "very frequent" (always or often) versus "less frequent" (sometimes, rarely, or never). All other diseases are dichotomous (yes/no)

[e] adOR: adjusted OR: Each disease and presbyphagia/dysphagia indicator was adjusted for gender, age, and the other diseases/indicators listed in the table

[f] yrs: years

[g] mo: months

difficulties, which stresses the importance of identifying these patients and facilitating their drug administration. The risk of difficulties in swallowing was associated with patient characteristics, was higher in females and younger patients and in the presence of dysphagia or associated co-morbidities.

The prevalence of difficulties in swallowing solid oral dosage forms in this study is in accordance with the results of an American internet survey [18] but is higher than in the Norwegian study, which was also conducted in primary care [17]. This may be due to the different response options to the key question of whether patients had difficulties in swallowing tablets and capsules in these studies. While in the Norwegian dichotomous questionnaire only yes and no were possible answers, our questionnaire offered a six point Likert scale. Hence, patients only rarely having these problems were also detected. In addition, our participants were given several examples of potential difficulties and, because patients with dysphagia often fail to perceive their impairment [27], such examples may have increased patients' awareness and influenced reporting.

Difficulties in swallowing tablets and capsules may be explained by three main factors: Functional and anatomical differences related to age and gender, functional and structural disorders, and physical characteristics of the dosage form itself.

In accordance with the Norwegian study, swallowing difficulties were more frequent in younger patients and women. This may be explained by physiological processes [28] and anatomical differences [29] with regard to the dimensions and function of mouth, pharynx, upper esophageal sphincter, and esophagus. Additionally, women are

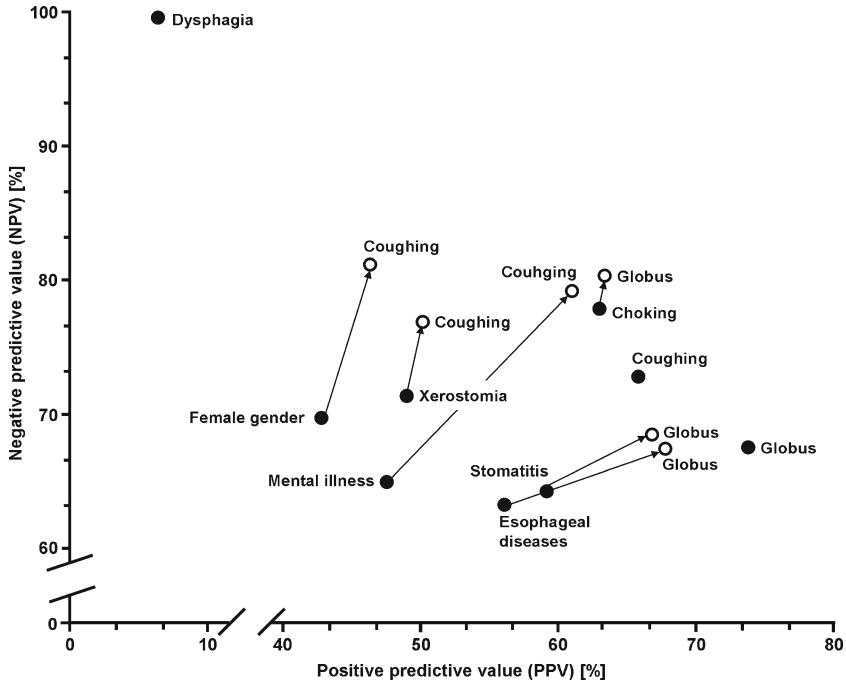

Fig. 4 Positive and negative predictive values of dysphagia indicators and diseases associated with dysphagia to identify difficulties in swallowing tablets and capsules in a general practice population of 1,051 consecutive patients. Solid symbols show the values for single indicators or diseases, open symbols connect to questions that further improved PPV

more prone to depression [30] and anxiety disorders [31] which may influence the frequency of swallowing problems as shown in institutionalized patients [32]. Therefore, gender differences may have also been influenced by an association between self-reported mental illness and swallowing difficulties reported in this study.

In general, dysphagia is expected to be more frequent in the elderly because of impaired control and delivery of the ingested bolus [10], delayed initiation of pharyngeal and laryngeal events [11], and cricopharyngeal muscle dysfunction. Therefore, it might actually be expected that older people have more problems swallowing tablets and capsules. But many patients with severe dysphagia are often in hospitals [33], nursing homes [15], or are visited by their GP at home. Thus, they attend physicians' offices less frequently and were not included in this study. Older patients without dysphagia, however, may experience fewer problems swallowing solid oral dosage forms because of training and habituation to drug intake and due to prolonged opening of the upper esophageal sphincter [34]. Additionally,

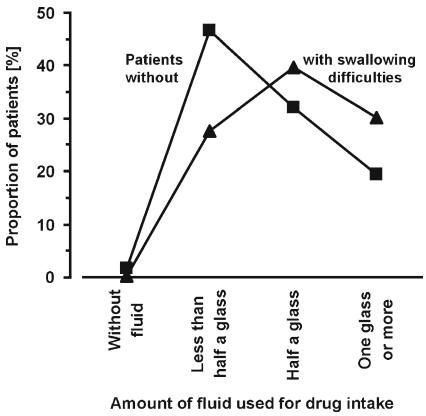

Fig. 5 Amount of fluid used to take drugs orally reported by 1,051 consecutive general practice patients with (37.4 %) and without (62.6 %) swallowing difficulties

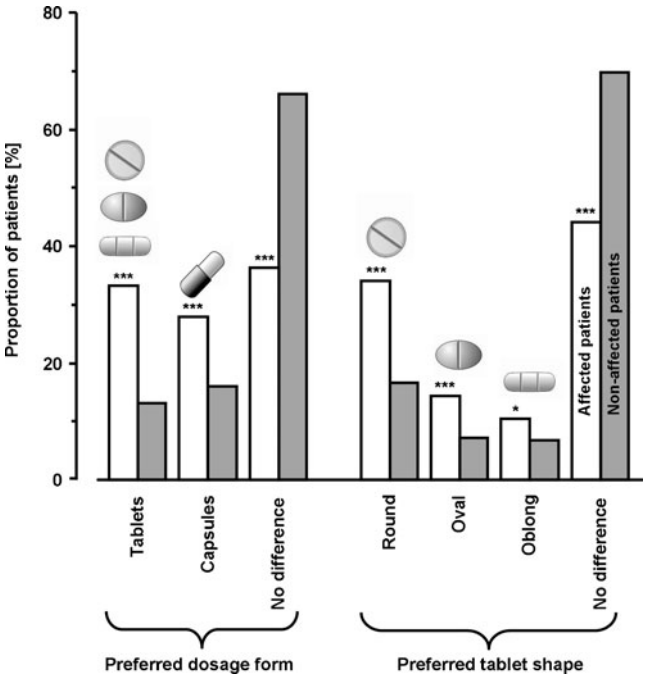

Fig. 6 Preferred types of dosage forms and tablet shapes in a general practice population with (37.4 %) and without (62.6 %) swallowing difficulties (N=1,051 consecutive patients)

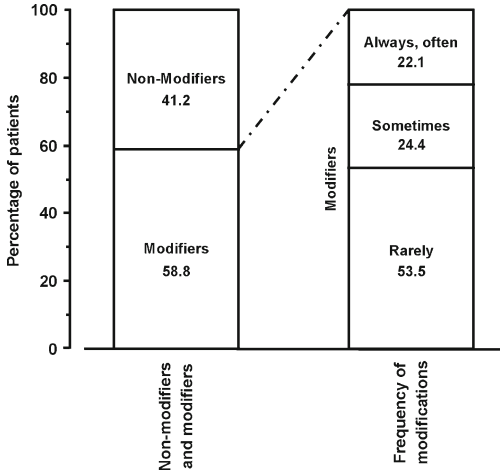

Fig. 7 Frequency of drug modifications by patients with swallowing difficulties (37.4 %) in a population of 1,051 consecutive general practice patients

pharyngeal sensitivity is reduced [35], probably causing less irritation.

Patients with dysphagia are at an increased risk for problems with swallowing tablets and capsules. Indeed, 39 % of dysphagic patients even had problems to swallow ODT (orally disintegrating technology) tablets [36].

High dysphagia prevalence rates are well established in stroke (29–81 %) [37, 38], dementia (45 %) [39], and Parkinson's disease (30–81 %) [40, 41]. Based on these findings, a strong association between difficulties in swallowing solid oral dosage forms and specific diseases was expected. However, when adjusted for gender, age, dysphagia indicators, and diseases likely to cause dysphagia, stroke and dementia were no longer associated with an increased risk. The missing association to stroke may be explained by the observation that swallowing dysfunction caused by stroke generally recovers within a short period of time [37, 42] and stroke in the patients of this study occurred 2 months to 30 years (median=3 years) before the survey. Acute stroke events in our population were rare. Similarly, despite the reported high prevalence of swallowing dysfunction in dementia [39] we did not find an elevated risk in such patients, probably because they were rare (only five patients). Furthermore, impaired swallowing is more common in advanced stages of dementia [43], e.g. in patients who are usually not able to answer questionnaires and thus were not enrolled.

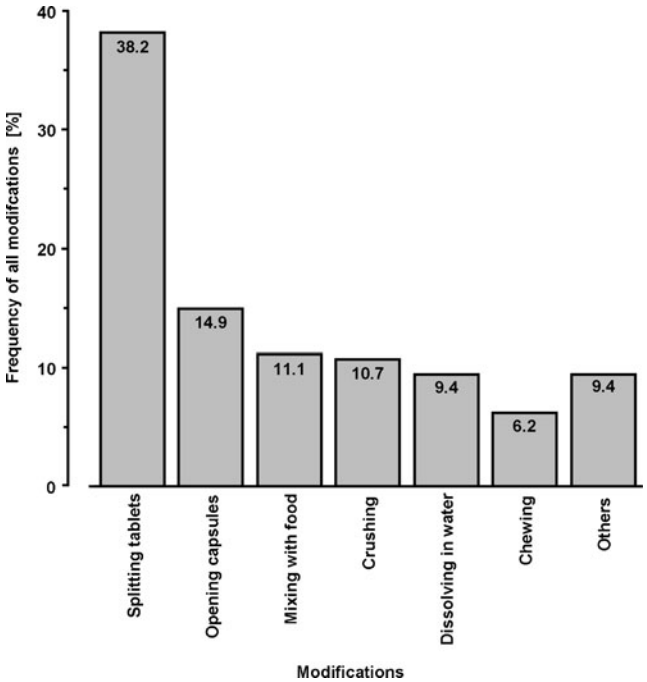

Fig. 8 Frequency of different types of drug modifications by patients with swallowing difficulties in a population of 1,051 consecutive general practice patients

Table 4 GPs'[a] reaction after being informed about patients' swallowing difficulties

GPs' reaction after being informed about patients' swallowing difficulties (n=54)	
GPs just changed drug	21 (38.9 %)
GPs just gave hints	8 (14.8 %)
GPs changed drug and gave hints	6 (11.1 %)
GPs did nothing at all	19 (35.2 %)

[a] GPs: general practitioners

An association of mental illness and dysphagia is also well documented in psychiatric inpatients. Risk factors seem to be symptoms of the mental illness itself as well as side effects of psychiatric drugs and the severity of the mental illness [32]. Hence, the prevalence of dysphagia seems to be smaller in patients attending day hospitals (27 %) in comparison to patients in long-term care facilities (31 %) or inpatient units (35 %) [44]. To our knowledge, there are no studies analyzing the relationship between dysphagia and mental illness in an ambulatory population, but our study results also suggest an association between self-reported mental illness and difficulties in swallowing tablets and capsules.

As recognized in earlier studies [17], size of solid dosage forms was often mentioned to cause swallowing difficulties in our questionnaires, too. On average, dimensions of drugs causing swallowing difficulties were about 11 % larger than the dimensions of corresponding drugs not causing problems thus indicating the importance of size. However, across dosage forms, size was clearly not the only determinant. For example, swallowing difficulties were only slightly more frequent with oval tablets even though their length was almost twice the diameter of round tablets. Similarly, hard gelatin capsules and soft gelatin capsules are up to 25 % longer than oblong tablets but the prevalence of swallowing

difficulties is only 10 % higher. Therefore, other characteristics are likely to contribute. Because tablets and capsules will rotate during swallowing to pass through the esophageal sphincter with the lowest possible resistance, a more important determinant of smooth esophageal passage should be the minimum cross-sectional area rather than the largest diameter of the solid oral dosage forms.

Our study revealed that in a large unselected ambulatory population of patients attending a GP's office difficulties of swallowing were reported by one in three patients and these patients were rather younger and more often female. An important question, therefore, is how they can be identified and what are practical options for improvement.

In a first attempt, identification of these patients has to be improved. In accordance with the American survey [18], only a small proportion (6.7 %) of the affected patients told their GPs about having swallowing difficulties and the majority of patients had never been asked about such problems by their GPs either. Therefore, it seems that physicians are unaware of the difficulties some of their patients are facing. Indeed, GPs did not diagnose 70.4 % of all affected patients and missed 59.1 % of patients who had such problems always, daily, or often. Therefore, special attention should be paid to women, patients with dysphagia, dysphagia indicators, or mental illness. In our study, patients at risk were easily identified by asking "Do you choke while eating or drinking?" and any answer other than "never" predicted difficulties in swallowing tablets and capsules with a sensitivity of 62.6 % and a specificity of 78.1 %. The sensitivity could even be increased by asking an additional question; either "Do you cough while eating or drinking?" or "Do you experience sensations like food being stuck in your throat while eating?" Thus, asking these questions seems to offer an easy way to identify affected patients.

The second question is how patients can be helped. As shown, shape and size of the dosage forms were linked to problems and the responses indicated that the swallowing technique was often inappropriate. Therefore, we expect that patients could be helped by switching to another solid dosage form (e.g. different shapes, capsules vs. tablets) or, preferably, to non solid oral dosage forms such as liquid therapeutic equivalents. Pharmacists can guide the appropriate choice of pharmaceutical formulations. In this context, both pharmacists and, especially, physicians would benefit from (likely electronic) decision support to achieve this objective easier.

Furthermore, important facts about medication application appeared to be unknown to the patients or were ignored by them. For instance, 40.7 % of all patients took their medicines with less than half a glass of water, 1.1 % even without any water. Similar results were found in patients attending German pharmacies when the amount of water was quantified that patients spontaneously used when swallowing their oral dosage forms at the pharmacy [45]. In that study, 36 % of the participants only took 100 ml of water or less which may have been more than the amount normally used because the patients were observed by a pharmacist [45]. To avoid damage to the esophagus by lodged tablets and capsules, several studies recommend to take tablets and capsules with at least 100 ml of water [46]. In many summaries of product characteristics and package leaflets a whole glass of water (= 200–250 ml) is suggested. In our study, patients with swallowing problems tended to take far more water than unaffected participants indicating that in most affected patients too little fluid was not the reason for their difficulties.

Another potentially more relevant application advice, however, appears to be largely unknown: the swallowing of capsules is easier with the head tilted forward [47, 48]. Capsules, whose specific gravity usually is less than one, will float on water. If patients tilt their head back while swallowing capsules they will swallow the water first leaving the capsule in the mouth or lodged in the throat. In contrast, tilting the head forward will help to transport the floating capsule to the hypopharynx and the esophagus, thus increasing the probability of successful swallowing [47]. In our investigation patients with difficulties tilted their head back more often when swallowing tablets and capsules than respondents not having any problems. An appropriate instruction could have helped 12 % (47/393) of the affected patients to swallow their capsules easier.

With respect to the clinical relevance of swallowing difficulties, two additional issues, modification of dosage forms and adherence, merit discussion. This study revealed that the more severe the patients' difficulties are, the more likely they will modify the dosage forms. It also confirms earlier observations that patients' knowledge about the hazards of modifying dosage forms is limited [19]. To ease swallowing, patients modify their medications [19, 20] in a way that may alter pharmacokinetics and thus safety and efficacy [49]. Indeed, up to 17 % of the modifications are potentially dangerous [21]. The destruction of coating sometimes causes mucosal damage or inactivation by gastric acid. The most dangerous alteration, however, is the destruction of modified release tablets or capsules, which may cause uncontrolled release of large quantities of the active ingredients (dose-dumping), overdosage, and may even be life-threatening [24]. Finally, particularly worrisome is the statement made by one in 11 patients that due to their swallowing difficulties they did not take the drug at all. Therefore, it is of importance for pharmacists to offer support by instructing patients in good drug application. They can give general information on how to take tablets and capsules correctly and also suggest and even train special swallowing techniques. Moreover, patients with swallowing difficulties should be advised which of their drugs can be modified safely and which modification technique is appropriate.

Limitations

Several limitations of this study need to be mentioned. First, consecutive patients who came to see the GP with or without an appointment were invited to take part in the study. Patients who just picked up a prescription were also supposed to be included. However, it cannot be ruled out that in larger practices with a high patient flow some of them were missed. Second, patients only rarely having swallowing difficulties were also detected which may have led to an overestimation of the relevance of these problems. But even if those patients were excluded the prevalence of swallowing difficulties would still be rather high (19.5 %). Finally, medical conditions such as stroke, dementia, and mental illness were ascertained through the questionnaires and were not verified by review of the medical records. This may have led to an underestimation of the association between diseases and swallowing difficulties due to missing information.

Conclusion

One in 11 general practice patients expressed frequent problems with swallowing medicines and a substantial fraction of these patients modified their drugs in a way that may alter pharmacokinetics and thus safety and efficacy. Additionally, nearly one in ten affected patients was non-adherent due to these problems. GPs grossly underestimated these difficulties. Given the prevalence of the problem and the fact that the majority of patients do not inform their doctor about such problems, physicians should regularly seek for swallowing difficulties to avoid non-adherence and dangerous modification of tablets and capsules by the patients. Special attention should be paid to specific patient groups at risk (e.g. women and patients with dysphagia or dysphagia indicators and mental illness) and swallowing difficulties should become part of the drug history.

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

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