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Marshmallow Root Extract for the Treatment of Irritative Cough: Two Surveys on Users' View on Effectiveness and Tolerability

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Keywords
Althaea officinalis · Cough · Safety · Effectiveness · Onset of effects

Summary
Background: Cough preparations containing aqueous marshmallow root extracts (*Althaea officinalis*) have a long history as medicinal products in Germany. The aim of the 2 prospective, non-interventional surveys reported here was to create a better documentation of the users' impression of the effectiveness and tolerability, and user satisfaction. **Methods:** Consumers (n = 822) buying either lozenges or syrup of the aqueous marshmallow root extract STW42 to treat their dry cough were recruited in pharmacies in 2 independently performed surveys. They were asked to fill in a questionnaire covering a treatment duration of 7 days so that the course of symptoms could be documented, and the overall effectiveness, tolerability and satisfaction assessed. **Results:** This consumer-reported outcome shows that both preparations showed a good effect with respect to the symptomatic treatment of oral or pharyngeal irritation and associated dry cough with a very rapid onset of effects, in the majority of cases within 10 min. The tolerability was very good (with only 3 minor adverse events for the syrup). **Conclusion:** The results of the surveys justify the long-established use of both marshmallow preparations for symptomatic treatment of dry cough.

Schlüsselwörter
Althaea officinalis · Husten · Sicherheit · Wirkung · Wirkeintritt

Zusammenfassung
Hintergrund: Hustenmittel auf der Basis wässriger Eibischwurzelextrakte (*Althaea officinalis*) haben in Deutschland eine lange Anwendungshistorie. Das Ziel der beiden Befragungen, über die hier berichtet wird, war die Erhebung der Anwendersicht zur praktischen Anwendbarkeit, Verträglichkeit und Zufriedenheit. **Methoden:** Kunden (n = 822), die entweder die Lutschpastillen oder den Sirup des wässrigen Eibischwurzelextrakts STW42 zur Behandlung ihres trockenen Hustens kauften, wurden in Apotheken in 2 unabhängig durchgeführten Umfragen rekrutiert. Sie wurden gebeten, einen Fragebogen zur Dokumentation des Symptomverlaufs über 7 Tage auszufüllen. Zudem sollten sie die Wirkung und Anwendungssicherheit sowie ihre Zufriedenheit mit der jeweiligen Zubereitung global bewerten. **Ergebnisse:** Diese kundenorientierte Auswertung zeigt, dass die Anwender eine sehr gute Wirkung bei Schleimhautreizungen im Mund- und Rachenraum und damit verbundenem trockenen Reizhusten sowie einen sehr schnellen Wirkungseintritt angaben, in der Mehrzahl der Fälle innerhalb von 10 min. Die Verträglichkeit war ausgezeichnet, die Anwenderzufriedenheit hoch. **Schlussfolgerung:** Die Ergebnisse der beiden Befragungen unterstützen die seit Langem bekannte Anwendung von Eibischzubereitungen in der symptomatischen Hustentherapie und bestätigen deren ausgezeichnete Verträglichkeit.

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Introduction

The common cold is one of the most frequent infectious diseases, with most adults suffering from an episode 2–4 times per year. Symptoms usually start with sore throat and dry cough, followed by rhinitis, headache, aching limbs, and productive cough. Finally, some days with dry cough are experienced. The dry cough is usually considered a major nuisance by the patients: it is burdensome and painful, and it interferes with sleeping patterns and recovery.

Approaches to the treatment of dry cough include, among others, the blockade of the cough reflex on the level of the corresponding receptors [1]. A further approach is the use of mucilaginous herbs such as plantain herb or marshmallow leaves or roots. The complex polysaccharides contained in marshmallow roots cover the irritated mucosa in the mouth and throat, thereby easing the cough reflex. The beneficial properties of mucilaginous extracts of *Althaea officinalis* for treating dry cough have received positive assessments, e.g. in the monographs of the German Commission E [2], the World Health Organization [3], European Scientific Cooperative on Phytotherapy [4], and the Herbal Medicinal Products Committee of the European Medicines Agency [5].

Typical indications for extracts of *A. officinalis* roots are the symptomatic treatment of oral or pharyngeal mucosal irritation and associated dry cough. The use of marshmallow preparations is well established in Germany for the treatment of dry cough in children and adolescents [6]. An observational study with 313 children aged 3 months to 12 years demonstrated the applicability of syrup containing marshmallow root extract for this age group [7]. The mechanism of action is attributed to the polysaccharides covering the irritated mucosa of the throat [8]. This polysaccharide film protects against irritants by supporting the function of the natural mucus layer. In addition to this purely mechanical effect, the polysaccharide covering of the mucosa also has a revitalizing effect on epithelial tissues [9], as aqueous marshmallow extracts and the isolated polysaccharides increase mucosa cell metabolism [9]. The antioxidative and local antimicrobial effects that have been demonstrated for marshmallow roots might also contribute to the overall efficacy. However, since these effects were detected using methanolic extracts, the results may not be transferable to aqueous marshmallow preparations [6, 10].

Marshmallow preparations are judged to be very safe treatment options. In Germany, where both surveys were performed, marshmallow preparations are on the list of medicinal products exempt from mandatory distribution through pharmacies due to their very good risk-benefit ratio. Physicians can therefore only recommend the therapeutic use of marshmallow preparations to their patients, especially to children. For this reason, a classical physician-based observational study is not likely to yield meaningful data. For cases in which the patients would rarely visit a physician, a study recruiting survey participants via a pharmacy is more feasible than a physician-based non-interventional study, as it reflects the local situation of the German drug market. The parameters for the assessment in the 2 surveys reported here were, however, the same as those that would have been selected in a physician-based observational study.

The patients were approached for participation only after their decision to purchase the marshmallow root preparations. There was no financial compensation for the patients or the pharmacist. Data from both surveys reflect the current usage of these preparations and are ranked as patient-reported outcome.

The aim of the study was to collect data on the effects of marshmallow preparations on individual symptoms of cough. Such results may be useful for the identification of patients with a specific occurrence of symptoms treatable with marshmallow preparations.

Methods

In 2 independent prospective, non-interventional surveys, consumers of 2 cough preparations (lozenges and syrup) containing an extract of *A. officinalis* received a questionnaire covering 7 days of treatment to document their view on the effectiveness and tolerability of the respective preparation.

Recruitment took place in the winter season 2014/2015 for the survey on the lozenges, and during the winter season 2015/2016 for the survey on the syrup. Users were recruited in pharmacies after having purchased the respective cough preparation, mostly upon recommendation of their physician. Completed and anonymized questionnaires were submitted by mail to the contract research organization (Winicker Norimed, Germany). As the surveys were performed as a consumer survey, a vote of the ethics committee was not applicable.

Examined Preparations

The preparations examined in the 2 surveys both contained preparations of *A. officinalis* root extract STW 42 (commercially available as 'Phytohustil Hustenreizstiller®', Bayer, Germany).

In 1 survey, the syrup was used (100 g containing 35.61 g marshmallow root extract as active constituent, extraction solvent purified water, drug-extract ratio (DER) 1:19.5–23.5). The recommended maximum daily dose for adults was 3–6 × 10 ml, as covered by the marketing authorization as a medicinal product and the recommendation of the monograph on Marshmallow by the German Commission E (10 g in a single dose).

In the other survey lozenges were used (1 lozenge containing 160 mg marshmallow root extract as active constituent, extraction solvent purified water, DER 3–9:1). The recommended maximum daily dose for adults was up to 10 lozenges, as covered by the marketing authorization. It corresponded to an average of 9.6 g marshmallow root equivalents in the maximum daily dose.

Study Parameters

Data recorded were age and sex of the participants, the concomitant use of other medications, the time between first occurrence of symptoms and the start of intake of the preparation, and the dose used by the patient. The user indicated the cough and cough-associated symptoms (dry cough, scratching in the throat, sore throat, feeling of dryness in the throat and bronchial pain) on a 5-point Likert scale (from 0 = symptom not present to 4 = very severe) at the beginning of the therapy. The users also rated their general well-being and satisfaction with the therapy on a 5-point Likert scale.

There was a slight difference in methodology for the 2 surveys: Whereas the patients using lozenges rated the severity of defined symptoms on every treatment day on a Likert scale ranging from 0 = not present, 1 = mild, 2 = moderate and 3 = strong to 4 = very strong, the patients in the syrup survey rated the individual symptom severity only at baseline, whereas on the following 7 days of treatment the rating referred to the improvement of symptoms, using a Likert scale ranging from 0 = no improvement, 1 = slight improvement, 2 = moderate improvement and 3 = good improvement to 4 = very good improvement.

Table 1. Demographic data

	Syrup	Lozenges
Survey population, n	516	306
Sex, %		
Female	67.3	71.6
Male	32.7	28.4
Mean age, years ± SD (range)	40.7 ± 16.3 (1–87)	44.8 ± 16.7 (7–87)
Age groups, % (n)		
0–17 years	4.5 (23)	1.6 (5)
18–29 years	22.2 (114)	21.6 (66)
30–49 years	44.2 (227)	37.3 (114)
> 49 years	29.0 (149)	39.5 (121)
Duration of symptoms before start of treatment, % (n)		
Up to 2 days	43.5 (224)	49.2 (150)
3–6 days	45.8 (236)	40.3 (123)
> 6 days	10.7 (55)	10.5 (32)
Daytime impairment by dry cough, % (n)	91.6 (471)	87.9 (268)
Nighttime impairment by dry cough, % (n)	89.7 (460)	80.5 (244)

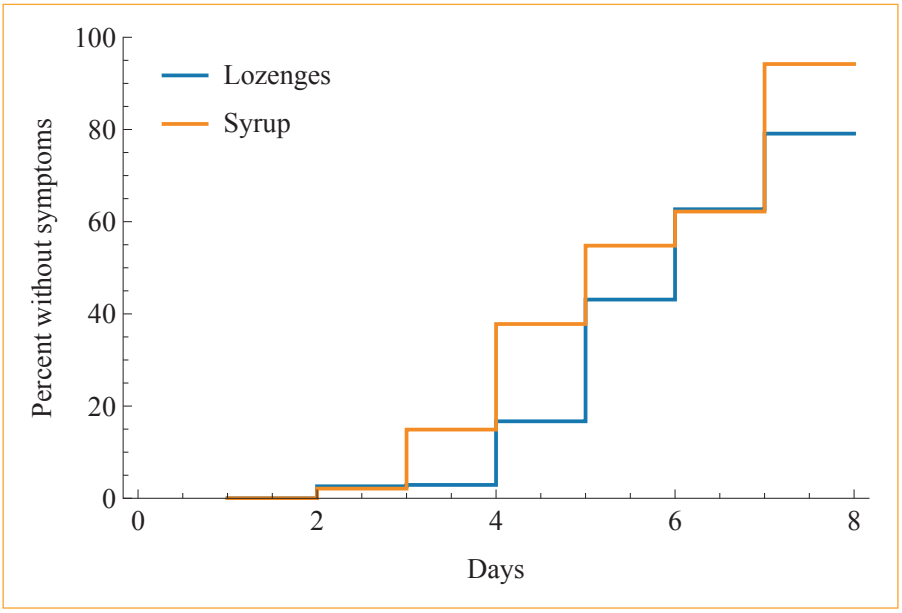

Fig. 1. Kaplan-Meier plots of days on which the patients no longer suffered from symptoms during treatment.

As a common factor to both surveys, the improvement of single symptoms was assessed in patients with an at least 'mild' severity (indication of 1 on the Likert scale) at baseline and at least 1 follow-up value during the survey. Results represent the percentage of patients experiencing an improvement, with confidence intervals for the incidence rate. In addition, the absolute changes of average severity of symptoms were calculated for the lozenges as a support for the presentation of the improvement and an indication of the clinical importance of the findings.

The onset of an effect was noted by the users as time from intake to first perceived effects in minutes. The duration of the effect was noted in hour ranges. Safety and tolerability were assessed by collecting reports of adverse events and additionally by the patients by an overall assessment of tolerability.

Statistics

The statistical analysis was conducted in all subjects with at least 1 documented intake of the respective preparation. Treatment duration until being free of complaints was analyzed using the Kaplan-Meier method, and the 95% confidence interval was calculated for each day; results were plotted using the median values (not presented). Symptom intensities were analyzed using frequency tables by day and by symptom. Missing values from early termination of application due to remission of symptoms were set to score '0' for the following days. Other missing values were replaced by the last observation carried forward. Data of effectiveness, safety/tolerability and satisfaction were also analyzed using frequency tables. Data management and descriptive analysis were performed using SAS v.9.2.

Results

A total of 822 users delivered questionnaires with at least 1 documented intake of the preparations examined in the surveys. The survey determining user behavior of the lozenges was conducted from September 8, 2014 to April 10, 2015 in Germany. Overall, 88 pharmacies recruited 306 subjects who documented intake of at

Table 2. Improvement of cough symptoms in percent, calculated for the survey participants with the individual symptom present at baseline; an average symptom score was calculated using a 5-point Likert rating scale; improvements refer to the reduction of the score relative to baseline

Symptom	Syrup		Lozenges	
	baseline, n[a]	improvement, % (95% CI for incidence rate)[b]	baseline, n[a]	improvement, % (95% CI for incidence rate)[b]
Dry cough	484	81.4 (77.6–84.4)	218	96.3 (92.9–98.4)
Scratching in the throat	440	74.8 (70.4–78.8)	181	92.3 (87.4–95.7)
Pain in the throat	344	68.3 (63.1–73.2)	122	95.1 (89.6–98.2)
Feeling of dryness in mouth and throat	421	72.4 (67.9–76.7)	154	95.5 (90.9–98.2)
Bronchial pain	285	67.7 (62.0–73.1)	74	94.6 (86.7–98.5)

[a]Subjects with at least mild symptom at baseline and at least 1 post-baseline score for the respective symptom.
[b]Improvement until end of treatment, at least slight improvement or decreased intensity score.
CI = confidence interval.

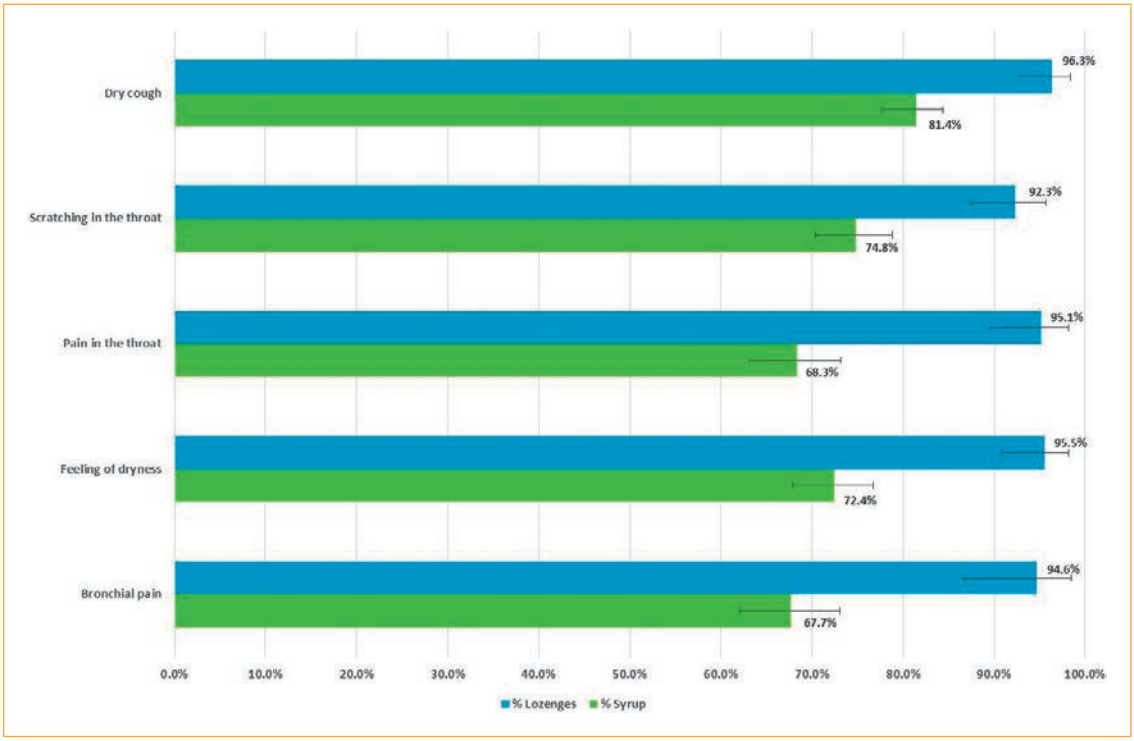

Fig. 2. Improvement of individual symptoms during the course of the treatment. An average symptom score was calculated using a 5-point Likert rating scale. Improvements refer to the reduction of the score relative to baseline.

least 1 lozenge and were hence included in the analysis. The survey with the syrup was conducted in Germany from October 15, 2015 to April 10, 2016. Overall, 152 pharmacies recruited 561 subjects. The vast majority of subjects (78.5%) bought the syrup following the recommendation of their pharmacist. Both surveys were conducted independently, but were similarly constructed. The demographic data were well-matched (table 1).

The daily doses taken were rather in the recommended medium range, with an average of 4.1 ± 1.4 lozenges or 31.9 ± 13.2 ml syrup. 283 participants (95.3%) using the lozenges and 473 patients using the syrup (91.7%) stopped the medication due to full remission. Of the individuals, 4.7% taking lozenges and 7.0% taking syrup indicated 'lack of efficacy' as a reason for early study termination, whereas no reason for discontinuation was given in 1.3% of cases in the syrup population. The Kaplan-Meier graphs showing the percentage of patients no longer suffering from symptoms is shown in figure 1.

For the treatment of dry cough, 363 (70.3%) participants used only the syrup, and 216 (70.6%) used only the lozenges. The remaining participants used various additional cough medications.

Development of Cough Symptoms

A distinct improvement of cough symptoms during therapy was detected in both surveys (table 2, fig. 2) in the patients indicating the presence of the individual symptom at baseline. Most importantly, all complaints originally assessed as 'very severe' were rated as 'moderate' to 'minor' after 4–6 days. The percentage of patients free of symptoms continuously increased during the course of the individual therapy. The median duration for recovery from symptoms was 5 days (calculated for the lozenges).

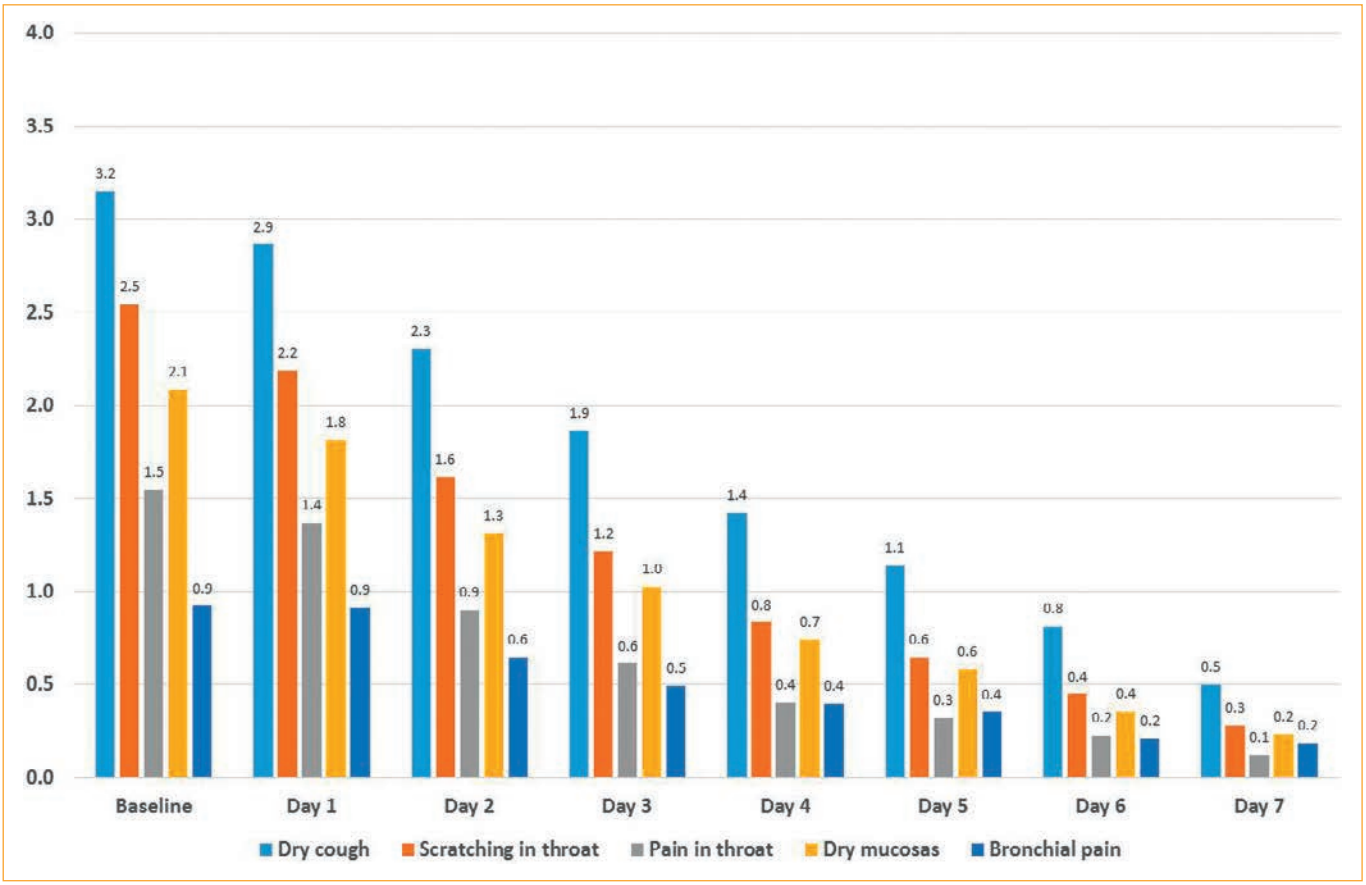

Fig. 3. Reduction of symptom severity in patients using the lozenges, calculated using a 5-point Likert rating scale in patients indicating the symptom at baseline (0 = no present, to 4 = strong severity).

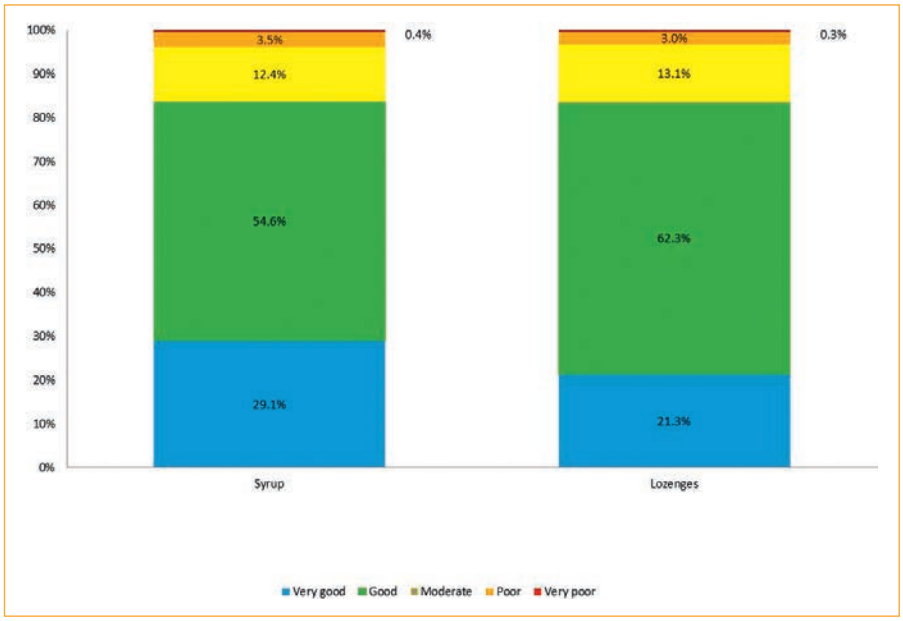

Fig. 4. Overall assessment of effectiveness of the 2 marshmallow preparations by the users. Syrup: n = 516; lozenges: n = 306.

The most important symptom indicated by the patients using the lozenges was irritative cough, followed by scratching in the throat and dry mucosas, with an average severity at baseline indicated as moderate to strong. Bronchial pain was not an important issue at baseline (fig. 3). All symptoms showed a distinct decline in severity, reaching an assessment of severity as 'mild' or less within 5 days of treatment.

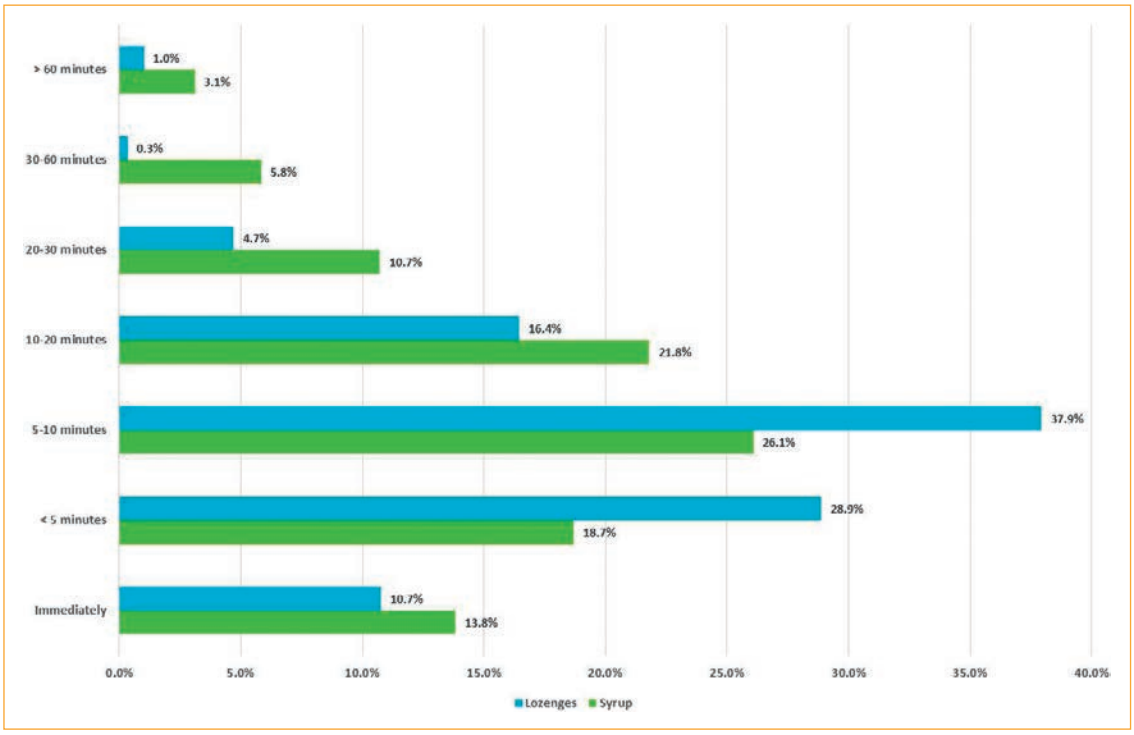

Fig. 5. Assessment of the onset of the effect of the preparation by the users.

The severity of symptoms at baseline was practically identical for the group using the syrup, with the exception of a slightly higher rate of severity for bronchial pain. The severity of irritative cough, scratching in the throat, dry mucosas and bronchial pain was assessed with an average of 3.3, 2.6, 1.7, 2.3 and 1.5 (with 0 = not present 1 = mild, 2 = moderate, 3 = strong and 4 = very strong as in the survey for the lozenges). The global effectiveness of the treatment was rated as 'good' or 'very good' by 83.7% of the participants (syrup) and 83.6% (lozenges) (fig. 4).

Onset of Action and Duration of Effect

The participants noted a rapid onset of the relief of symptoms: 58.6% using the syrup and 77.5% using lozenges reported a relief within 10 min after application. The majority of participants (72.8% using the syrup and 76.4% using the lozenges) reported a duration of effects between 1 and 4 h post application (fig. 5).

User Satisfaction

Considering user satisfaction, 84.9% of the syrup and 90.2% of the lozenges users were 'pleased' or 'very pleased' with the treatment; 95.7% (syrup) and 96.4% (lozenges) of the users stated that they could imagine using the preparation for treatment of oral or pharyngeal irritation associated with dry cough in the future.

Safety of Application

During the survey with the lozenges, no adverse events were reported. With the syrup, subjects reported bloating (1 case), slight abdominal discomfort (1 case); and poor tolerability without further details. The tolerability of the preparation was rated as 'good' or 'very good' by 98.8% of participants using the syrup and by 96.7% of those using the lozenges.

Discussion

It is essential to know and understand the needs of the users by measuring their experience and satisfaction. Especially in the area of non-prescribed over-the-counter (OTC) medication, the patient-reported outcome is the key source of information available, as usually no physician is involved in the treatment. In the presented independent surveys, the users completed questionnaires handed over by their pharmacist. A downside of this approach is that such data can be neither verified nor corrected, and certain values usually documented in clinical trials cannot be obtained through such a design. The uncontrolled study design would, for example, not allow the replacement of missing values by the worst case imputation method, which is why the method of last known value carried over was applied. With a self-healing condition such as cough, this approach should not favor the study outcome, as the carry-over of the last value will assume no further improvement of symptoms.

Overall, however, such surveys still allow drawing conclusions on patient experience and product safety with OTC products, especially in cases where the regulatory product classification excludes the participation and professional opinion of healthcare professionals in treatment. Marshmallow preparations are regulated as pure OTC products in Germany, with sales explicitly allowed outside of pharmacies. Any information on safety of application and clinical usefulness must therefore be sought from the patients themselves. Such information is important for the physicians as a foundation for recommendation to the patient.

The results of the 2 patient surveys reveal a very good acceptance and tolerability of the 2 OTC preparations containing the aqueous marshmallow root extract STW 42 for the treatment of oral or

pharyngeal irritation and associated dry cough, presented as syrup and as lozenges. At the first glance, it may seem that the effect of the lozenges was stronger. However, a head-to-head comparison of the surveys for the 2 products is not feasible due to the slightly different methodology. The dosing of both preparations corresponded to the officially authorized declaration, which is effectively higher with the lozenges. It could be speculated that this difference in dosing (up to 14.4 g marshmallow root equivalents with the lozenges and up to 1 g with the syrup) and possibly the prolonged time of contact with the mucosa through the use of lozenges may have contributed to the stronger reduction of symptoms observed with this application form, but again such a definite conclusion cannot be drawn from this study due to the differences in study design.

In the case of the survey with the lozenges, the analysis of the impact of the medication on the severity of individual symptoms showed a clinically important and rapid improvement. As the calculated findings for improvement of symptoms did not differ between groups, and as the starting values for severity of individual symptoms were practically identical in both surveys, it may be expected that the observations for severity of individual symptoms on each treatment day would also have been observed with the use of the syrup.

As the surveys were uncontrolled, the results could not be compared with the usual course of an episode of irritative cough. The average duration of cough episodes has, however, been found to be 17.8 days in a systematic review of placebo groups in controlled studies and untreated controls [11]. The findings of the presented survey, especially the quick response to treatment, must therefore be considered clinically highly important.

Within this study, the effect of the co-medication used by approximately 30% of the study population was not assessed through a subgroup analysis, because the additional medication taken by the individual patients was very heterogeneous. This may be considered a downside in the evaluation of the study results. The findings on the usage of the syrup did, however, closely correspond to, and confirm data from, an observational study in children [7]. All cough and cough-related symptoms examined improved well over the treatment period of 7 days. The overall user satisfaction was very high.

The generally accepted mechanism of action of marshmallow root preparations is the formation of a protective film over the irritated mucosa of the mouth and throat. This mode of action is consistent with the observation of a quick onset of effect of both STW 42-containing formulations of marshmallow root extract: syrup and lozenges. Overall, the outcomes of both surveys reflect the significance of the application of marshmallow root extract products and indicate their high value in the treatment of dry cough.

Disclosure Statement

C.F. participated in the planning of the surveys and is an employee of the sponsor. M.S. and K.K. declare no conflict of interest.

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