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Effects of *Pelargonium sidoides* extract EPs 7630 on acute cough and quality of life – a meta-analysis of randomized, placebo-controlled trials

Peter Kardos,[1] Walter Lehmacher,[2] Andrea Zimmermann,[3] Juliette Brandes-Schramm,[3] Petra Funk,[3] Heinrich Matthys,[4] Wolfgang Kamin[5,6]

[1]Group Practice and Centre Allergy, Respiratory and Sleep Medicine at Red Cross Maingau Hospital, Frankfurt am Main, Germany
[2]Emeritus, University of Cologne, Institute of Medical Statistics, Informatics and Epidemiology, Cologne, Germany
[3]Research & Development Department, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany
[4]Medical Director Emeritus, Department of Pneumology, University Hospital Freiburg, Freiburg, Germany
[5]Children's Hospital, Evangelic Hospital Hamm GmbH, Hamm, Germany
[6]Faculty of Medicine, Pomeranian Medical University, Szczecin, Poland

ABSTRACT

Background: Cough is a leading symptom of viral acute respiratory infections such as acute bronchitis (AB) and the common cold (CC), which can be debilitating and may persist for several weeks. We investigated whether treatment with *Pelargonium* extract EPs 7630 may reduce cough and improve disease-related quality of life (QoL).

Methods: We performed a meta-analysis of randomized, placebo-controlled trials investigating the efficacy of EPs 7630 in AB or CC. Efficacy analyses included change from baseline in a cough intensity score, remission of cough, and disease-associated impairments of QoL.

Results: Data of 2,195 participants from 11 trials (3 in children/adolescents with AB, 3 in adults with AB, 5 in adults with CC) were eligible. In children/adolescents with AB, 79.6% of participants treated with EPs 7630 and 41% treated with placebo showed a reduction in the intensity of cough by at least 50% of baseline values at day 7 [meta-analysis rate/risk ratio (RR), EPs 7630 / placebo: 1.86 (95% CI: 1.34; 2.95)], and 18.0% *vs* 5.5% presented with complete remission of cough [RR: 2.91 (95% CI: 1.26; 6.72)]. In adults with AB, 88.7% of participants in the EPs 7630 group and 47.6% in the placebo group showed a ≥50% response for cough intensity [RR: 2.13 (95% CI: 1.37; 3.31)], while 26.0% *vs* 6.3% did not cough any more at day 7 [RR: 5.00 [95% CI: 3.10; 8.07)]. Cough scale results were supported by significant improvements over placebo in the pursuit of normal daily activities and other QoL measures. In CC, 56.8% of participants treated with EPs 7630 and 38.8% treated with placebo showed a ≥50% cough intensity reduction [RR: 1.40 (95% CI: 1.19; 1.65)] at day 5, while 26.1% *versus* 18.4% showed complete remission of cough for EPs 7630 and placebo, respectively [RR: 1.40 (95% CI: 1.06; 1.84)]. CC-associated pain/discomfort and impairment of usual activities were no longer present in 41.5% and 48.8% of participants treated with EPs 7630 compared to less than 40% of patients in the placebo group.

Conclusions: The results show that EPs 7630 reduces the burden and leads to earlier remission of cough. Advantages for EPs 7630 were also reflected in self-rated measures of disease-associated QoL. Of note, patients treated with the herbal product felt able to resume their usual daily activities sooner.

Key words: Acute bronchitis; acute cough; acute respiratory tract infection; common cold; EPs 7630; meta-analysis; *Pelargonium*; quality of life.

Correspondence: Petra Funk, Research & Development Department, Dr. Willmar Schwabe GmbH & Co. KG, Willmar-Schwabe-Str. 4, 76227 Karlsruhe, Germany. E-mail: petra.funk@schwabe.de

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Ethics approval and consent to participate: The studies included into our meta-analysis were reviewed and approved by the responsible competent, independent ethics committees. Further details can be found in the original publications.

Consent for publication: Not applicable.

Introduction

Viral acute respiratory tract infections (ARTIs) are the most prevalent diseases in primary care, regardless of patient age and sex [1-3]. In ARTIs such as acute bronchitis (AB) and the common cold (CC), cough is a leading symptom [4], causing over 50% of new patient attendance in primary care and being the major source of consultation in pharmacies [5-7].

Proposed mechanisms of virus-induced cough in patients with ARTI include effects on the airway epithelium such as cytokine release by inflamed epithelial cells associated with increased neurotransmitter and neural receptor levels and reduced activity of neutral endopeptidases, as well as effects on cholinergic motor pathways like bronchoconstriction and airway hyperresponsiveness caused by increased leukotriene production and mucus hypersecretion through superficial goblet cells and submucosal glands [6,8,9].

Presentations connected with ARTIs commonly overlap [10], and for AB and CC, for example, it was even suggested that both terms may describe different aspects of the same syndrome [6]. CC is characterized by rhinorrhea, sore throat, sneezing, chilliness, and mainly dry cough. In AB, cough is the prominent symptom, typically dry during the initial 2-3 days, then productive for up to 2 weeks, and then again dry, sometimes lasting for several weeks [6,11]. In CC, however, mucus hypersecretion may also occur during the first 2-3 days [6], and coughing may be provoked by postnasal drip as well [12,13]. It is therefore increasingly recognized that distinguishing between cough associated with AB or CC may hardly be practicable [6,14], especially since the implications of the distinction for disease management are minimal and treatment is often initiated in practice based on clinical symptoms alone and without establishing a specific diagnosis [15].

Symptoms associated with viral ARTIs may range from annoying to incapacitating. In adults, they are a major source of decreased productivity and lost work time [16]. In children, cough in particular affects sleep, the ability to play, and school performance, and it causes disruption and anxiety for parents and other household members [5,17]. For ARTIs, current management strategies aim at symptom control, *i.e.*, a reduction in symptom severity and duration, as well as patient education [18]. The effectiveness of these strategies is highly increased with early intervention, as an early treatment start reduces the chances of developing full-blown disease, decreases symptom severity, and reduces viral transmission [19].

Dry cough causes an irritation of the already affected mucous membranes and leads to increased mucus production, and thus antitussive treatment is indicated [20]. Productive cough should, however, not be suppressed as it enables the evacuation of mucus from the bronchi [21].

EPs 7630[1] is a proprietary extract from the roots of *Pelargonium sidoides*. Medicinal products containing EPs 7630 have been approved for the treatment of AB and/or CC in countries in Asia, Europe, Australia, as well as in Central and South America. Its pharmacological properties have been described in detail [22,23]. In short, EPs 7630 has antibacterial and antiviral effects that are mediated partly via stimulation of host defense mechanisms such as release of tumor necrosis factor alpha and nitric oxides, the stimulation of interferon-β, and an increase in natural killer cell activity. In addition, EPs 7630 was shown to inhibit the replication of influenza A virus strains (H1N1, H3N2), respiratory syncytial virus, human coronavirus (HCoV) 229E, parainfluenza 3 virus, and coxsackie virus A9 [24]. In this context, it was also shown that EPs 7630 treatment outcomes of common cold patients with confirmed HCoV infection were as favorable as in patients with other viral infections [25]. Moreover, EPs 7630 was shown to reduce docking proteins for rhinovirus and to simultaneously increase the expression of host defense systems [26]. In animal models, EPs 7630 caused a dose-dependent reduction of the frequency and extension of the latency of irritant-induced dry coughing and had a likewise dose-dependent bronchosecretolytic effect without suppression of productive cough [27]. Furthermore, in several different *in vitro* experiments, EPs 7630 was shown to inhibit SARS-CoV-2 replication and modulate innate immune responses in the human lung cell line Calu-3 [28]. Systematic reviews and meta-analyses of randomized controlled trials support the efficacy and safety of the herbal extract in ARTIs [23,29-36].

While previous research was mainly directed towards the overall symptom burden caused by ARTIs, the effects of EPs 7630 on cough, the most debilitating and persistent symptom in AB and CC, have not been systematically evaluated in detail. This meta-analysis was performed to close this gap.

Methods

Study eligibility criteria, search strategy

For inclusion into our meta-analysis, studies had to be double-blind, randomized and placebo-controlled, and had to investigate the efficacy of treatment of AB or CC with EPs 7630 in children, adolescents, or adults. Moreover, studies had to report an investigator rating of cough severity as well as a patient reported outcome for disease-related quality of life (QoL).

To identify studies performed with EPs 7630 in the indications of interest, a free-text search of all fields of the MEDLINE database as well as of the ClinicalTrials.gov and the ISRCTN registries for any records entered before 10 November 2020 was performed, that included the search terms 'EPs 7630' or 'Pelargonium' in combination with 'acute bronchitis' or 'common cold' (no other search restrictions applied). Further data on published and unpublished trials with EPs 7630 in the indications of AB and CC were then obtained from the manufacturer of the herbal extract.

Ethical conduct

Trials could be included into this meta-analysis if they were reported to have been planned, performed, and analyzed according to the principles of Good Clinical Practice and the Declaration of Helsinki. This included testimony of approval of the study protocol and of other applicable study documents by the competent independent ethics committees and authorities as well as of obtaining written informed consent from all trial participants or their legal guardians.

[1]*EPs® 7630 is the active ingredient of the pharmaceutical product Umckaloabo® (ISO Arzneimittel, Ettlingen, Germany). It is available in over 40 countries under various trade names, e.g., Kaloba®, Umcka®, Umckalor®, and Renikan®.*

Interventions

EPs 7630 is an extract from the roots of *Pelargonium sidoides* (1:8-10), extraction solvent: ethanol 11% (w/w), which is marketed as a solution, as tablets, and as a syrup for children. Only the marketed as well as higher doses were to be considered in our analyses.

Outcomes of interest

For meta-analysis, data on cough intensity as rated by the investigator was sought from the rating scale that was most commonly used across the eligible studies. For AB, data on cough severity for our analysis therefore derived from the applicable item of the investigator-rated Bronchitis Severity Scale (BSS). For CC, information on cough derived from the observer-rated Cold Intensity Score (CIS). Both items rate the severity of cough on a verbal rating scale ranging from 0 ('absent') to 4 points ('very severe'). Day 7 had previously been identified as the most commonly reported time point of pre-defined day of follow up in most ARTIs [29,31]. We therefore considered absolute intraindividual score change of the severity of cough at day 7 compared to baseline the most appropriate outcome in AB. In the subset of CC trials, day 5 was considered relevant in accordance with earlier research [35]. Moreover, the proportions of participants with complete remission of cough as well as with an at least 50% cough score reduction as compared to baseline were determined for those patients reporting cough at baseline. For analysis of disease-related quality of life (QoL), we also sought data from the rating scale that was most commonly used across eligible studies. We therefore analyzed health-related QoL as assessed by means of the European Quality of Life 5 Dimensions 3 Level (EQ-5D-3L) questionnaire, a descriptive system that comprises the 5 dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each of which is self-rated on a 3-point scale ranging from 1 (no problems) to 3 (extreme problems) [37]. In trials performed in children and adolescents, EQ-5D-3L was not assessed. We therefore analyzed data derived from the Children's Health Status Questionnaire [Fragebogen zum Gesundheitszustand für Kinder (FGK)] [38], a 6 item QoL questionnaire. By means of this questionnaire, participants of the studies or their caregivers were asked to rate each of the items ('Everything is too much for me', 'I am feeling ill', 'I am scared', 'I have trouble playing or learning', 'I sleep badly', 'I have problems getting into conversation with others') on a scale ranging from 1 to 5 points with values being represented by verbalizations ('not at all' through 'very distinctive') as well as by matching pictograms of faces.

Separately for each item of the applicable scales, we analyzed the proportion of participants with complete remission at day 7 (AB trials) or day 5 (CC trials), relative to the number of participants with any impairment at baseline.

Statistical methods

Analyses were performed in accordance with a prospectively defined analysis plan.

Age and sex of patients were analyzed using descriptive statistics. Meta-analyses were based on the individual participant data of the included trial using a two-step approach according to which the outcomes of interest were first analyzed individually within each study and then combined using 'traditional' meta-analysis [39]. During the first step, cough scores were determined by calculating the intraindividual difference between day 7 and day 5, respectively, and baseline. These mean values and their estimated standard deviations were then used as input for the meta-analyses performed in the second step. Rating scales were analyzed as continuous outcomes. For dichotomous outcomes such as response and remission of cough symptoms and further items, meta-analyses were based on the within-study number of patients with the event of interest and the total number of patients. In this context, response was defined as an at least 50% reduction of the symptom severity or of other items with respect to QoL limitations as compared to baseline. Consequently, higher rates imply a more favorable outcome (e.g., higher share of patients without any cough symptom). Resulting risk ratios greater than 1.0 therefore indicate a heightened probability of remission under EPs 7630 intake compared to placebo, for example, and therefore a beneficial effect of the herbal extract. To reflect this context, we speak of rate/risk ratios in the following.

Heterogeneity between the trials was assessed using the I^2 statistic in accordance with the criteria proposed in the Cochrane Handbook for Systematic Reviews of Interventions [40]. For $I^2 > 5\%$, random effects meta-analyses were performed, and fixed effects meta-analyses otherwise. For all meta-analyses, two-sided $p \leq 0.05$ were considered descriptively significant.

The analyses were based on the full analysis set as defined in the protocols of the eligible trials with the following restriction if necessary: Separately for each outcome, only patients were included into the meta-analysis who presented with the respective symptom at baseline. Missing data were imputed by carrying forward the last valid observation. In the case of studies with one placebo arm but multiple eligible EPs 7630 dosage arms, patients from the placebo group were *post-hoc* divided into different placebo groups in order to include reasonably independent trial parts for meta-analyses for each of the active treatment arms to be analyzed. This is a procedure described for the comparison of the remaining dosage groups to placebo in the literature [41].

Meta-analyses were computed with RevMan software version 5.2 [42] and higher. All other analyses were performed in SAS statistical software version 9.3 and higher.

Results

Search results and study populations

Literature searches identified a total of 52 records, one of which was a duplicate. Among the 51 remaining publications and registry entries, 42 were excluded during screening for reasons indicated in Figure 1.

The remaining 9 publications presented results from 11 randomized, placebo-controlled, multicenter phase III clinical trials. The individual participant data available for analysis was made available by the manufacturer of EPs 7630. Six of the trials were performed in AB, with 3 of them assessing children and adolescents [43-45] while the remaining 3 trials investigated adults [46-48]. The 5 trials identified in the indication CC included only adult patients. Among these trials, 1 investigated 2 different doses of EPs 7630 and the results were published separately [49,50]. The remaining 4 trials were published in an original paper [51] or were included in a systematic review of the efficacy and tolerability of EPs 7630 in CC [35].

The main characteristics of the eligible trials are shown in Table 1. All trials in AB had a randomized treatment phase of 7 days and used the BSS as the primary outcome measure for efficacy at day 7. Quality of life at day 7 was assessed by the EQ-5D-3L (adults) and the FGK (children and adolescents), respectively. One of the adult trials, study F, was a dose-finding trial. Among the pediatric trials, studies A and C included children and adolescents

between 1 and 18 years of age, with dosage selection according to age. Study B was a dose-finding trial that included participants aged 6-18 years. For inclusion, pediatric and adult participants had to be suffering from symptoms of AB for a period not exceeding 48 hours and had to present with a BSS total score ≥5 points at screening. In the trials in CC, eligible patients had to be suffering from the primary symptoms nasal drainage and sore throat and from at least 1 (studies G and H) or 2 (studies I through K) of the secondary symptoms nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, muscle aches, and fever, or from 1 of the primary symptoms and at least 3 secondary symptoms. The time allowed between the onset of the first symptoms and study inclusion was 24-48 hours for studies G and H and up to 72 hours for studies I through K. All trials in CC had a randomized treatment phase of 10 days and applied the CIS at day 5 as the primary outcome measure for efficacy. Quality of life at day 5 was assessed by the EQ-5D-3L.

In total, 2,195 (AB 1,363; CC 832) trial participants were included into the meta-analyses, 1,201 of whom were exposed to EPs 7630 (AB 785; CC 416).

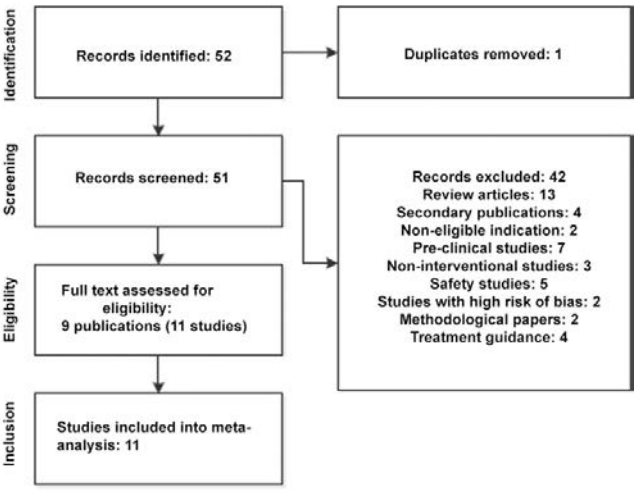

Figure 1. Search results and selection of eligible trials.

Table 1. Characteristics of trials and patients included in the meta-analysis.

Indication, study population	Trial	Formulation	Treatment; daily EPs 7630 dosage	Age*	Female#	Participants°
Acute bronchitis, children and adolescents						
	A (Kamin *et al.*, 2010) [43]	Liquid	EPs 7630; dosage acc. to age§	9.4±5.0	51.5%	103
			Placebo	9.5±5.1	53.6%	97
	B^ (Kamin *et al.*, 2010) [44]	Tablets	EPs 7630; 3 x 20 mg	12.9±3.7	48.5%	99
			EPs 7630; 3 x 30 mg	12.6±3.7	47.5%	99
			Placebo	12.7±3.7	49.5%	101
	C (Kamin *et al.*, 2012) [45]	Liquid	EPs 7630; dosage acc. to age§	8.7±4.8	51.4%	111
			Placebo	9.2±5.2	49.5%	109
Acute bronchitis, adults						
	D (Chuchalin *et al.*, 2005) [46]	Liquid	EPs 7630; 3 x 30 drops	36.2±13.0	76.6%	64
			Placebo	35.9±13.2	63.3%	60
	E (Matthys *et al.*, 2007) [47]	Liquid	EPs 7630; 3 x 30 drops	38.3±13.4	72.2%	108
			Placebo	36.5±11.4	78.9%	109
	F‡ (Matthys *et al.*, 2010) [48]	Tablets	EPs 7630; 3 x 20 mg	41.8±13.2	76.2%	101
			EPs 7630; 3 x 30 mg	38.8±13.7	72.0%	100
			Placebo	38.5±12.6	61.8%	102
Common cold, adults						
	G (Lizogub *et al.*, 2007) [49]	Liquid	EPs 7630; 3 x 30 drops	34.5±10.6	69.2%	52
			Placebo	37.4±10.5	68.6%	51
	G (Riley *et al.*, 2018) [50]	Liquid	EPs 7630; 3 x 60 drops	36.8±9.9	73.1%	52
			Placebo	33.8±10.8	76.9%	52
	H (Riley *et al.*, 2019) [51]	Tablets	EPs 7630; 3 x 40 mg	35.0±10.9	75.5%	53
			Placebo	37.7±10.5	78.8%	52
	I (Schapowal *et al.*, 2019) [35]	Liquid	EPs 7630; 3 x 30 drops	37.1±13.6	66.7%	99
			Placebo	37.1±12.5	65.3%	101
	J (Schapowal *et al.*, 2019) [35]	Liquid	EPs 7630; 3 x 30 drops	44.8±14.1	63.4%	101
			Placebo	46.2±14.1	70.0%	100
	K (Schapowal *et al.*, 2019) [35]	Tablets	EPs 7630; 3 x 20 mg	32.6±11.0	44.1%	59
			Placebo	33.3±10.6	48.3%	60

*Years, mean±SD; #percentage of patients (%); °full analysis set; §1-6 years: 3 x 10 drops; 7-12 years: 3 x 20 drops; >12 years: 3 x 30 drops; ^dose finding study; a treatment group with EPs 7630 3 x 10 mg/day was not included into the meta-analysis.

Acute bronchitis, children and adolescents

Trials A through C performed in the indication AB included a total of 719 children and adolescents, 412 of whom received EPs 7630. Cough intensity at baseline was comparable for EPs 7630 and placebo, with a meta-analysis difference of 0.04 points; 95% confidence interval, 95% CI: -0.04, 0.13 points on a 5-point scale. The main results of the meta-analysis for change in cough intensity between baseline and day 7 are shown in Figure 2. The reduction in cough intensity was significantly more pronounced in participants randomized to EPs 7630 across all trials (point estimate for difference: 0.6 points) as well as in the single trials A, C, and in the 3 x 30 mg/d group of trial B. Substantial heterogeneity between the trials was attributable to differences between the effect sizes for the individual treatment comparisons - all of which favored EPs 7630 - and not differences regarding the direction of the effect. Confidence intervals for the point estimates in trial B were wider than those for trials A and C because the placebo group of trial B had to be split to enable the comparison for the two different dosages of EPs 7630. Across all trials, 328/412 (79.6%) children and adolescents treated with EPs 7630 and 126/307 (41.0%) in the placebo group showed a reduction in the cough intensity score by at least 50% of the baseline value [meta-analysis rate/risk ratio (RR), EPs 7630 / placebo: 1.86; 95% CI: 1.34, 2.59], and 74/412 (18.0%) and 17/307 (5.5%) presented with complete remission of cough (RR: 2.91; 95% CI: 1.26, 6.72).

Regarding the subjective impairment of well-being assessed with the Children's Health Status Questionnaire, impairment at baseline was particularly common for a general feeling of illness, impaired sleep, and having trouble playing or learning. At day 7, each of the 6 items of the scale showed a significantly higher proportion of children and adolescents with complete remission of impairment in the EPs 7630 group as compared to placebo ($p<0.05$; Table 2). For 5 of the 6 items ('Everything is too much for me', 'I am feeling ill', 'I have trouble playing or learning', 'I sleep badly'), participants treated with EPs 7630 showed a reduction of the relative risk of persistent impairment at day 7 at or above 50%.

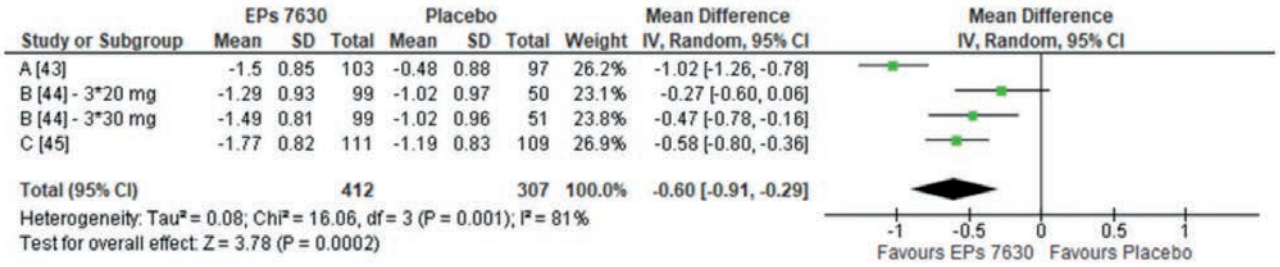

Figure 2. **Cough intensity – meta-analysis results for change between baseline and day 7 in children and adolescents suffering from acute bronchitis.**

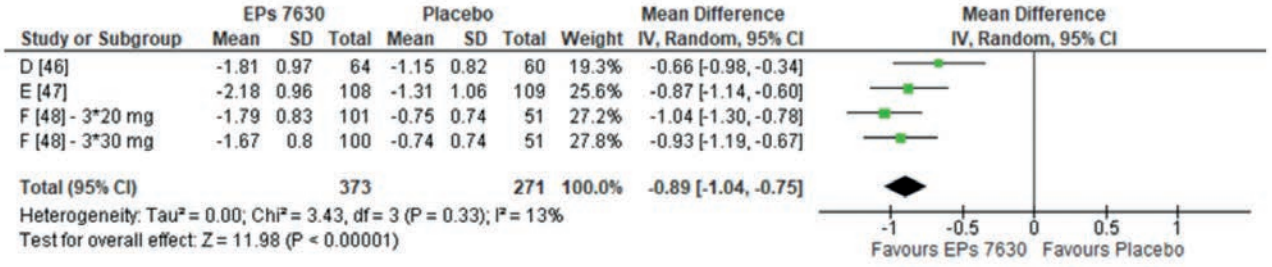

Figure 3. **Cough intensity – meta-analysis results for change between baseline and day 7 in adults suffering from acute bronchitis.**

Table 2. **Children's Health Status Questionnaire – proportion of children/adolescents with acute bronchitis showing complete symptom remission at treatment day 7, based on participants with symptoms at baseline (pooled data from trials A, B, and C).**

Item	Participants in remission / participants with impairment at baseline		Meta-analysis rate/risk ratio (EPs 7630 / placebo), 95% CI
	EPs 7630	Placebo	
Everything is too much	192/304 (63.2%)	87/239 (36.4%)	1.74 [1.41; 2.13]
Feeling ill	232/398 (58.3%)	91/301 (30.2%)	1.99 [1.48; 2.69]
Being frightened	189/205 (92.2%)	103/147 (70.1%)	1.32 [1.17; 1.48]
Trouble playing or learning	227/337 (67.4%)	117/271 (43.2%)	1.55 [1.20; 2.00]
Sleeping badly	302/357 (84.6%)	147/267 (55.1%)	1.48 [1.26; 1.75]
Trouble getting into conversation	228/313 (72.8%)	125/249 (50.2%)	1.38 [1.21; 1.57]

Acute bronchitis, adults

Adult participants randomized to EPs 7630 (n=373) in trials D, E and F showed slightly less severe coughing at baseline than those in the placebo group (n=271; meta-analysis difference: 0.11 points; 95% CI: 0.00, 0.21 points).

Main results for change in cough intensity between baseline and day 7 are presented in Figure 3. In each trial analyzed individually as well as in the meta-analysis, where a point estimate for the treatment group difference of 0.89 points was observed, patients treated with EPs 7630 showed a significantly more pronounced reduction in the cough intensity score than those in the placebo group. No important heterogeneity of results was observed (I^2=13%). In the pooled data set in adults with AB from all trials, 331/373 (88.7%) patients treated with EPs 7630 and 129/271 (47.6%) patients in the placebo group showed a reduction of cough intensity by at least 50% compared to baseline (meta-analysis RR, EPs 7630 / placebo: 2.13; 95% CI: 1.37, 3.31) while 97/373 (26.0%) and 17/271 (6.3%) did not cough any more at day 7 (RR: 5.00; 95% CI: 3.10, 8.07).

Among the items of the EQ-5D QoL, the areas with the largest proportions of participants impaired at baseline were 'Usual activities' and 'Pain/discomfort'. These were also those items for which remission rate ratios indicated the largest advantages for EPs 7630 over placebo. Table 3 shows that remission rates >80% were observed for all EQ-5D items in the EPs 7630 group, whereas 4 of the 5 items showed remission rates below 65% in the placebo group. Of note, the proportion of patients with baseline impairment of usual activities who were able to fully resume their daily activities by the end of the 1-week treatment was about twice as large in the EPs 7630 group as in the placebo group, and about 18% of the participants treated with the herbal product still showed impairment compared to more than 58% of the initially impaired patients randomized to placebo.

The common cold

Unlike the trials in AB, the participants of trials G through K performed in CC were not strictly required to be suffering from coughing for inclusion. At baseline, coughing was observed in 345 and in 348 participants for EPs 7630 and placebo, respectively, and with comparable intensity in both groups (meta-analysis difference: 0.04 points; 95% CI: -0.07, 0.15 points). Study G, which investigated two different dosages of EPs 7630 liquid, included a dedicated placebo arm for each dosage (due to the different numbers of drops to be administered; see Table 1) so that no splitting of the placebo group had to be performed.

Regarding the reduction of cough intensity during the 5 days' randomized treatment, Figure 4 shows a significant advantage favoring EPs 7630 over placebo, by a meta-analysis mean value difference of 0.34 points (point estimate). Significant treatment group differences were also observed for both dosages of EPs 7630 in study G while all other eligible studies in CC showed non-significant differences favoring the herbal product. The figure also indicates non-substantial heterogeneity between the trials (I^2=25%) that was attributable to different effect sizes while all within-study treatment group differences favored EPs 7630. Based on the pooled data from all eligible trials in CC, 196/345 participants treated with EPs 7630 (56.8%) and 135/348 in the placebo group (38.8%) showed a reduction of treatment day 5 cough intensity by at least 50% compared to baseline. In the associated meta-

Table 3. EQ-5D-3L questionnaire – proportion of adults with acute bronchitis showing complete symptom remission at treatment day 5, based on participants with symptoms at baseline (pooled data from trials D, E, and F).

Item	Participants in remission / participants with impairment at baseline		Meta-analysis rate/risk ratio (EPs 7630 / placebo), 95% CI
	EPs 7630	Placebo	
Mobility	199/237 (84.0%)	113/177 (63.8%)	1.36 [1.07; 1.74]
Self-care	134/142 (94.4%)	68/90 (75.6%)	1.25 [1.11; 1.42]
Usual activities	284/346 (82.1%)	99/239 (41.4%)	2.20 [1.41; 3.45]
Pain / discomfort	293/351 (83.5%)	145/258 (56.2%)	1.63 [1.09; 2.45]
Anxiety / depression	169/199 (84.9%)	91/149 (61.1%)	1.35 [1.15; 1.58]

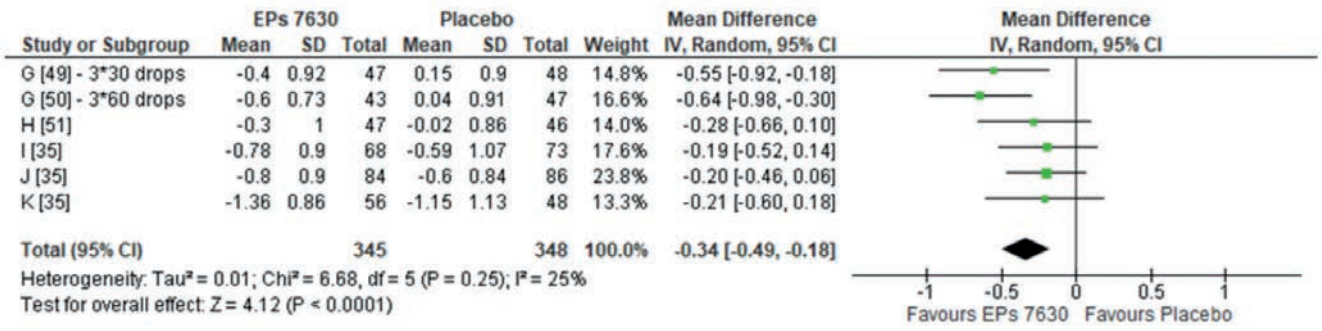

Figure 4. Cough intensity – meta-analysis results for change between baseline and day 5 in adults suffering from the common cold.

Table 4. **EQ-5D-3L questionnaire – proportion of participants with the common cold showing complete symptom remission at treatment day 5, based on participants with symptoms at baseline (pooled data from trials G, H, I, J, and K).**

Item	Participants in remission / participants with impairment at baseline		Meta-analysis rate/risk ratio (EPs 7630 / placebo), 95% CI
	EPs 7630	Placebo	
Mobility	112/157 (71.3%)	95/166 (57.2%)	1.27 [1.03; 1.55]
Self-care	123/152 (80.9%)	94/153 (61.4%)	1.29 [1.00; 1.67]
Usual activities	120/246 (48.8%)	97/254 (38.2%)	1.33 [1.02; 1.73]
Pain / discomfort	141/340 (41.5%)	131/339 (38.6%)	1.13 [0.82; 1.56]
Anxiety / depression	104/158 (65.8%)	101/183 (55.2%)	1.12 [0.88; 1.44]

analysis, a RR (EPs 7630 / placebo) of 1.40; 95% CI: 1.19, 1.65 favoring EPs 7630 was determined. Moreover, 90/345 (26.1%) and 64/348 (18.4%) of the participants showed complete remission of cough for EPs 7630 and placebo, respectively (RR: 1.40; 95% CI: 1.06, 1.84).

Table 4 shows that the subjectively most prominent CC-associated annoyances at baseline were pain and discomfort as well as impairment of usual activities. After 5 days of randomized treatment, these were no longer present in 41.5% (pain/discomfort) and 48,8% (usual activities impairment) of the participants treated with EPs 7630 and in less than 40% of those randomized to placebo. The proportion of participants whose complaints had fully subsided by day 5 was always larger for EPs 7630 than for placebo. Statistically significant effects were found in the meta-analyses for 'Mobility' and 'Usual activities' ($p<0.05$).

Discussion

Coughing is a leading symptom of viral ARTIs such as AB and CC which may have an annoying and grueling effect on children and adults alike, causing interference with essential activities of daily living and disruption of sleep in patients and their nuclear families [5,16,17]. In ARTIs, cough may persist for several weeks, causing persistent distress and reduced well-being [16,52]. It is therefore a clinically important treatment target.

This meta-analysis shows that *Pelargonium sidoides* extract EPs 7630 is efficacious in both reducing intensity and accelerating remission of cough related to AB in children, adolescents, and adults. Moreover, compared to placebo, participants treated with EPs 7630 showed higher restauration rates in subjective well-being and usual activities of daily living. In adults with CC (no studies with the herbal product in children with CC were available for analysis), EPs 7630 also had a significant antitussive effect although its advantages over placebo in QoL outcomes were somewhat less pronounced. The latter may be attributable to the fact that impairing symptoms in CC tend to be more diverse than in AB, and that persistent impairment of subjective well-being may thus have been caused by CC-associated symptoms other than cough.

Even though the assessment of cough intensity used in our meta-analyses was derived from a validated scale [53,54], the clinical importance of the observed treatment group difference in a single-item score, albeit statistically significant, may be difficult to assess. In the absence of a validated minimal clinically important difference, a 50% reduction of the initial symptom load as well as the proportion of participants with complete symptom remission are considered commonly used and face-valid criteria of treatment success [31]. The results of the meta-analyses indicate that the proportions of participants with a 50% reduction of cough intensity at treatment day 7 in the EPs 7630 group exceeded those in the placebo group by factors 1.9 and 2.1 for children/adolescents and for adults with AB, respectively. At the same, the proportions of participants with complete cough remission under EPs 7630 exceeded those for placebo by factors 2.9 and 5.0. This can be considered indicative of a clinically meaningful treatment effect. The interpretation is consistent with the results for the participant-rated QoL measures which indicate that the effects of EPs 7630 on AB were also perceived to be patient-relevant. For CC, meta-analysis results show an advantage for the herbal product by factor 1.4 for both a 50% reduction of cough intensity and complete remission of cough by treatment day 5, which also supports the relevance of the score reduction.

The results for cough reduction are also consistent with those of recent meta-analyses for EPs 7630 in AB and CC where similar improvements were observed when analyzing the total scores of the symptom scales from which the cough scale was taken [33,35]. The meta-analyses published earlier additionally show the good tolerability and safety of EPs 7630 in acute respiratory tract infections [33,35,36].

Corresponding to the assessment of the primary endpoint in the eligible trials, the assessment of coughing intensity took place at day 7 (AB) and 5 (CC) after treatment initiation, respectively. It is not surprising that the majority of study participants had not yet achieved a complete remission at these time points, as cough may persist for several weeks and thus longer than any other symptom of ARTIs [11,52].

The results of our meta-analyses demonstrate that, at a comparatively early stage of treatment, the vast majority of patients treated with EPs 7630 (but not of those randomized to placebo) already presented with a meaningful reduction of cough intensity by more than 50% of the baseline value. These findings are consistent with those obtained by Bao and colleagues who demonstrated in an animal model that EPs 7630, in the therapeutically relevant dose range, exerts an antitussive effect on dry cough and also has a significant secretolytic effect that may contribute to its cough-inhibiting action without suppression of the important defense mechanism of productive cough [27]. This also supports the recommendation made by Längler *et al*., who stated that EPs 7630 could be used as first-line therapy for uncomplicated respiratory tract infections such as AB, CC, and acute tonsillopharyngitis in children [55]. Our results indicate that this recommendation may also apply to adult patients.

Conclusions

Our meta-analysis shows that 7 days' treatment with EPs 7630 is associated with a clinically meaningful reduction of cough intensity as well as with improved disease-associated QoL and daily functioning in adult patients suffering from AB and also in pediatric patients. In CC, adults suffering from cough also showed a meaningful symptom reduction under EPs 7630.

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Abbreviations

AB:	acute bronchitis;
ARTIs:	acute respiratory tract infections;
BSS:	Bronchitis Severity Scale;
CC:	common cold;
95% CI:	95% confidence interval;
CIS:	Cold Intensity Score;
COPD:	chronic obstructive pulmonary disease;
EQ-5D-3L:	European Quality of Life 5 Dimensions 3 Level;
HCoV:	human coronavirus;
ISRCTN:	International Standard Randomised Controlled Trial Number;
QoL:	quality of life;
RR:	rate/risk ratio.

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