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Influence of EPs 7630 on Antipyretic Comedication and Recovery from Acute Tonsillopharyngitis in Children: A Meta-analysis of Randomized, Placebo-Controlled, Clinical Trials

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Abstract

Objective Acute tonsillopharyngitis (ATP) is a common, seasonal infection of predominantly viral origin. Management is aimed at shortening the course of the disease and restoring the comfort of the patient. We performed a meta-analysis to investigate whether treatment with the *Pelargonium sidoides* extract EPs 7630 reduces the use of antipyretic comedication (i.e., acetaminophen) in children suffering from ATP.

Methods Studies were identified from clinical trial registries and medical literature. Randomized, placebo-controlled, clinical trials investigating EPs 7630 in children with ATP and reporting the coadministration of paracetamol were eligible. Based on the raw data of eligible trials, we analyzed cumulative paracetamol use, as well as the ability to attend school at the end of treatment. Three trials including a total of 345 children aged 6 to 10 years and suffering from non-β-hemolytic streptococcal ATP were identified and eligible. Children were administered EPs 7630 or placebo for 6 days.

Results Compared with placebo, EPs 7630 reduced the cumulative paracetamol dose by an average of 449 mg (95% confidence interval [CI]: 252–646 mg; $p < 0.001$). A total of 19.1% (EPs 7630) and 71.5% (placebo) of children were still unable to attend school at the end of the treatment (risk ratio = 0.28; 95% CI: 0.16–0.48; $p < 0.001$).

Conclusion Our meta-analysis demonstrates that EPs 7630 reduced the use of antipyretic comedication and accelerated recovery.

Keywords
- acute tonsillopharyngitis
- children
- meta-analysis
- paracetamol
- *Pelargonium sidoides*

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Introduction

Acute tonsillopharyngitis (ATP) is a very common, seasonal infective disorder characterized by an inflammation of the pharynx and the palatine tonsils which occurs in all age groups and accounts for approximately 5% of all visits in pediatric care.[1] Common symptoms of ATP include sore throat, dysphagia, red pharynx, enlarged tonsils covered with a yellow, blood-tinged exudate, fever with sudden onset, malaise, gastrointestinal complaints (such as vomiting, abdominal pain, and diarrhea), halitosis, rhinorrhea, hoarseness, and cough.[2] ATP of viral origin, as found in more than 60% of all cases in children, more often includes rhinorrhea, cough, diarrhea, and hoarseness as compared with bacterial ATP.[2] For viral ATP, rhinovirus, coronavirus, and adenovirus are the most common causes.[3] Bacterial ATP is most commonly caused by group A streptococcus (GAS) whose prevalence in children of all ages with ATP has been estimated at 37%.[1] Tonsils and adenoids have been shown to harbor bacterial and viral pathogens, which may increase the potential for recurrence and chronification,[4] and a reliable distinction between viral and bacterial ATP is often not easily achieved in the pediatric population.[5] According to current disease management guidelines from Europe and North America, antibiotic treatment should only be administered in cases of confirmed bacterial infection. In all other cases, only symptomatic treatment is recommended.[6,7]

Symptomatic treatment is aimed at relieving the symptom burden caused by ATP and includes analgesia, hydration, and rest. Mainly motivated by improving the child's overall comfort, analgesic drugs, such as paracetamol (acetaminophen), are widely used.[8] In addition to analgesia, paracetamol also has an antipyretic effect, although ATP is usually not associated with fever in a range requiring antipyretic treatment. Fever has been shown to inhibit the replication of viruses and to exert a stimulating effect on the patient's immune system. Consequently, antipyresis may even prolong the duration of infectious diseases.[8–12] Moreover, paracetamol has been linked with a risk of certain rare but potentially harmful side effects and unintentional overdose in children.[13–15]

Pelargonium sidoides extract EPs 7630 (EPs® 7630 is the active ingredient of the product Umckaloabo®, ISO-Arzneimittel, Ettlingen, Germany) is a herbal preparation from the roots of *P. sidoides* and used in adults and in children from the age of 1 year for the treatment of respiratory tract infections in several countries in Europe, Central and South America, Asia, and Australia. EPs 7630 was shown to support the immune response of the organism by a stimulation of the release of tumor necrosis factor-α and nitric oxides, the stimulation of interferon-β, and an increase in natural killer cell activity.[16–19] In vitro and in vivo EPs 7630 and several of its isolated constituents demonstrated an antiviral activity by interfering with the replication of several seasonal influenza A virus strains, respiratory syncytial virus, human coronavirus, parainfluenza virus, and coxsackievirus,[20,21] while direct antipyretic effects have not been reported for EPs 7630. A comprehensive presentation of the pharmacological properties of EPs 7630 has been published elsewhere.[22]

In randomized, placebo-controlled, clinical trials performed in children and adults, EPs 7630 was efficacious in acute respiratory tract infections including ATP.[22–30] A review of the safety and tolerability based on more than 8,000 patients exposed to EPs 7630 shows the favorable safety profile of this herbal preparation.[31]

As the avoidance of unwanted and mostly unnecessary antipyresis is an important clinical advantage, particularly in children suffering from ATP, EPs 7630 may be an interesting therapeutic option. We report on a meta-analysis performed to investigate whether symptomatic treatment of children suffering from ATP with EPs 7630 may reduce the coadministration of paracetamol, an issue which has not been subjected to an in-depth analysis so far. Moreover, we also assessed whether EPs 7630 administration is associated with faster recovery of the children's ability to attend school.

Materials and Methods

We performed a meta-analysis of double-blind, randomized, placebo-controlled, clinical trials investigating treatment with EPs 7630 in children with ATP.

EPs 7630 is an extract from the roots of *P. sidoides*, drug-extract ratio = 1:8–10, extraction solvent = ethanol 11% (w/w), which is available as a liquid solution with a recommended dose of 3×10 drops/d for children aged 1 to 5 years, 3×20 drops/d for children aged 6 to 12 years, and 3×30 drops/d for adults and adolescents over 12 years. A film-coated tablet formulation for adolescents over 12 years, as well as adults, and a syrup formulation for children aged 1 to 12 years are also available but were not used in any of the identified ATP studies.

Study selection criteria, as well as the statistical methods, were defined prospectively. Eligible studies had to investigate the use of EPs 7630 in children with ATP while allowing the concomitant use of paracetamol whose administered amount had to be reported. No other restrictions were applied.

Search terms included the combination of "EPs 7630" or "Umckaloabo" with "tonsillopharyngitis" or "sore throat" and with "placebo controlled." Searches were performed using clinical trial registries (ISRCTN; ClinTrials.gov) and literature databases (MEDLINE; EMBASE) and completed in April 2017. Titles, abstracts, and keywords were considered in the search.

Outcome measures of interest were the investigational treatment administered, paracetamol consumption, and inability to attend school due to ATP. For a basic characterization of the trial populations, we also extracted patient age and sex.

The meta-analysis included all clinical trials meeting the eligibility criteria above without further restrictions. Analyses were based on the individual patient data of the eligible trials which were provided by the study sponsor.

All analyses were performed based on the efficacy analysis datasets of the eligible trials. Sample characteristics were analyzed using descriptive statistics. For the cumulative dose of paracetamol, a meta-analysis was performed by computing the difference between the mean values of the treatment groups and the associated 95% confidence intervals (CIs) in the original scale. Since the eligible trials used identical

prescriptions for paracetamol dosing, cumulative paracetamol use could be analyzed on the original scale instead of using a standardized but more abstract effect size measure. Moreover, we determined the percentage of children who were unable to attend school at the end of the scheduled treatment period and performed a meta-analysis based on risk ratios and their 95% CIs. The I^2 statistic and a χ^2 test were used for assessing heterogeneity between trials. Pooled meta-analysis estimates were obtained by using random effect models in case of $I^2 > 5\%$, and fixed effect models otherwise. For all meta-analyses, Review Manager Version 5.2 software was used.[32] Treatment differences were considered descriptively significant if the 95% CI of the point estimate did not include the value of 0 for differences between means or the value of 1 for risk ratios, corresponding to a descriptive, two-sided p-value of ≤ 0.05.

The cumulative paracetamol dose of patients withdrawn from the trial prematurely was calculated for the period between the start of the investigational treatment and the date of withdrawal. The ability to attend school was assessed based on the last valid information.

Results

The results of our database search are shown in ►**Fig. 1**. Searches in MEDLINE, EMBASE, as well as in the ISRCTN and ClinicalTrials.gov registries, produced a total of 14 records. One additional review was identified which mentioned studies with EPs 7630 in ATP even though it did not match our search terms. Four matches were duplicates and therefore excluded. Furthermore, eight records, which had been retrieved because sore throat or tonsillopharyngitis mentioned in the title or in the abstract, were excluded during screening, based on further information extracted from the data source: one excluded record referred to an ongoing trial and reported no results, three excluded records were publications of clinical trials with EPs 7630 in indications other than ATP (i.e., acute bronchitis, the common cold) and in a different study population (adults),[33–35] two were review articles which did not add new studies beyond those which we had already identified,[22,29] one excluded record referred to a conference paper of a safety review of EPs 7630 and did not report results on paracetamol use,[36] and one excluded record was a brief report from a press conference.[37] The remaining three trials met our eligibility criteria also after full-text review and were therefore included into our meta-analysis.[38–40]

The three trials that met our eligibility criteria were performed in Ukraine according to similar protocols and included a total of 173 children treated with EPs 7630 and 172 treated with placebo. All trials included girls and boys aged 6 to10 years with ATP signs and symptoms persisting for ≤48 hours. Moreover, eligible children had to have a negative rapid antigen-detection test for β-hemolytic streptococci, as well as a total score of ≥8 points on a five-item tonsillopharyngitis symptom scale (TSS; severity assessment of the symptoms dysphagia, sore throat, salivation, redness, and fever on a 4-point scale; total score range: 0–15 points) in trials A and C, or ≥6 points on a 7-item TSS (severity assessment of the symptoms dysphagia, sore throat, salivation, redness, coating left, coating right, and fever on a 4-point scale; total score range: 0–21 points) in trial B. In all three trials, fever was scored as <37.5°C = 0, 37.5°C to <38.5°C = 1, 38.5°C to <39.5°C = 2, and ≥39.5°C = 3. The other symptoms were assessed by the following categories: not present = 0, mild = 1, moderate = 2, and severe = 3. Duration of treatment as scheduled was 6 days in all included trials. Other main characteristics of the trials are shown in ►**Table 1**.

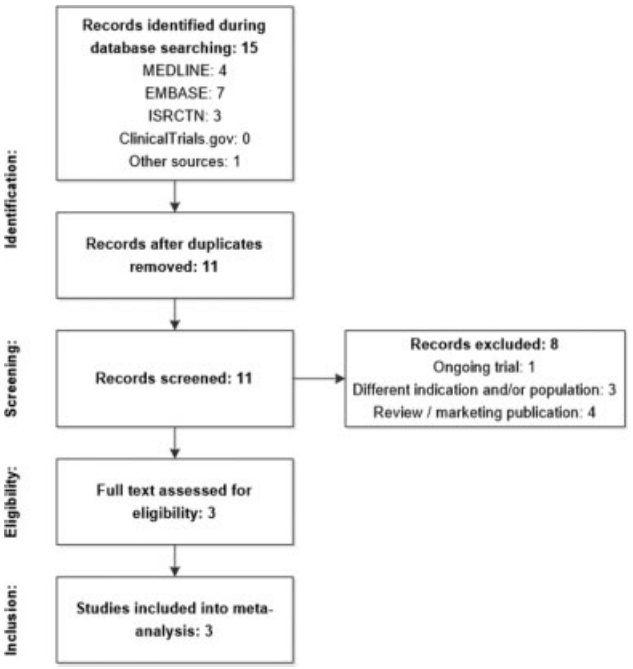

Fig. 1 Selection of clinical trials for meta-analysis.

In case of fever ≥38.5°C, the concomitant administration of paracetamol suppositories was allowed on days 0 through 4 after the start of randomized treatment in all three trials, up to a maximum daily dose of 3 × 500 mg. All administered doses had to be documented. Any other concomitant medication with potential impact on the study outcomes and/or on the course of ATP (e.g., antibiotic treatment) was not allowed.

Basic demographic data of the patients is shown in ►**Table 2**. All children except 1 were between 6 and 9 years old and with negligible mean value differences between the treatment groups.

All clinical trials were performed according to an adaptive, group-sequential design. On the level of all individual studies included into the analysis, bias was controlled by requiring the inclusion of consecutive patients who were eligible and for whom informed consent could be obtained, by randomized treatment assignment, and by blinding of the study drugs (including blinded outcome assessments). We asked the manufacturer for data of all randomized, placebo-controlled, clinical trials conducted to investigate the administration of EPs 7630 to children suffering from ATP. Since our search included both published and unpublished clinical trials conducted in the indication and population of interest, a publication bias can be excluded. Moreover, as all clinical trials reported data on our predefined outcome measures, no

Table 1 Main characteristics of eligible trials

Trial: Author (year)	Duration of treatment (daily dose)	Primary efficacy outcome measure	Number of patients[a]	
			EPs 7630	Placebo
A: Bereznoy et al (2003)[38]	6 days (3 × 20 drops)	TSS (5 items): difference between baseline and day 4	73	70
B: Timen et al (2015)[39]	6 days (day 1–2: 20 drops hourly while awake; day 3–6: 3×20 drops)	Response: TSS (7 items) ≤ 4 points at day 4	40	38
C: Berezhnoi et al (2016)[40]	6 days (3 × 20 drops)	TSS (5 items): difference between baseline and day 4	60	64

Abbreviation: TSS, tonsillopharyngitis symptom score.
[a]Primary efficacy analysis dataset (full-analysis set).

within-study selective reporting could have occurred for the outcomes of interest.

In trials A[38] and C,[40] the predefined primary outcome measure was the change of the TSS total score between baseline and treatment day 4. The children treated with EPs 7630 in trial A showed a decrease in the TSS total score by 7.1 ± 2.1 points compared with 2.5 ± 3.6 points in children treated with placebo (95% CI for mean value difference: 3.3–5.7 points favoring EPs 7630). In trial C, the TSS total score (mean ± standard deviation) decreased by 6.7 ± 2.7 and 3.3 ± 4.2 points for EPs 7630 and placebo, respectively, with a 95% CI for the mean value difference ranging from 2.0 to 5.2 points favoring EPs 7630. The primary outcome measure of trial B[39] was the percentage of children presenting with a TSS ≤4 points at day 4 of randomized treatment. This criterion was met by 40 (90%) participants in the EPs 7630 group and by 38 (44.7%) participants in the placebo group ($p < 0.001$; Fisher's exact test).

The main meta-analysis results of cumulative paracetamol use during participation in the clinical trials are shown in ►**Fig. 2**. Although the mean cumulative dose of paracetamol ranged between 425 and 1,623 mg for EPs 7630 and between 724 and 2,043 mg for placebo, the treatment effects observed in the analyzed trials were homogeneous ($I^2 = 0.0\%$; $p = 0.59$).

As compared with placebo, cumulative consumption of paracetamol in the EPs 7630 group was reduced by an average of 449 mg (95% CI: 252–646 mg; $p < 0.001$), with individual study mean values ranging between reductions of 299 and 558 mg corresponding to reductions by 41% of the cumulative amount in the placebo group in trials B and C and by 21% in trial A where the absolute cumulative dose of paracetamol was the highest.

►**Fig. 3** shows that the number of children unable to attend school at treatment end (identified as "events") was significantly higher for placebo as compared with EPs 7630 for all three studies included into the meta-analysis. In the pooled dataset, the event rates observed were 19.1% (33/173 patients) and 71.5% (123/172 patients) for treatment with EPs 7630 and placebo, respectively, and a meta-analysis risk ratio of 0.28 (95% CI: 0.16–0.48; $p < 0.001$).

The I^2 value of 66% (χ^2 test: $p = 0.05$) determined in this meta-analysis indicates moderate to substantial heterogeneity between the results of the trials.[41] ►**Fig. 3** shows, however, that heterogeneity was attributable to between-trial differences in the magnitude, not by direction of the treatment

Table 2 Demographic data

Trial: Author (year)	Treatment group	Age (y) Mean ± SD (range)	Sex (absolute and relative number of patients)	
			Female *n* (%)	Male *n* (%)
A: Bereznoy et al (2003)[38]	EPs 7630	7.6 ± 1.3 (6–10)	40 (54.8)	33 (45.2)
	Placebo	7.5 ± 1.1 (6–9)	30 (42.9)	40 (57.1)
B: Timen et al (2015)[39]	EPs 7630	7.4 ± 1.2 (6–9)	26 (65.0)	14 (35.0)
	Placebo	7.7 ± 1.2 (6–9)	18 (47.4)	20 (52.6)
C: Berezhnoi et al (2016)[40]	EPs 7630	7.6 ± 1.1 (6–9)	29 (48.3)	31 (51.7)
	Placebo	7.4 ± 1.2 (6–9)	28 (43.8)	36 (56.3)
Pooled data of trials A, B, and C	EPs 7630	7.5 ± 1.2 (6–10)	95 (54.9)	78 (45.1)
	Placebo	7.5 ± 1.2 (6–9)	76 (44.2)	96 (55.8)

Abbreviation: SD, standard deviation.

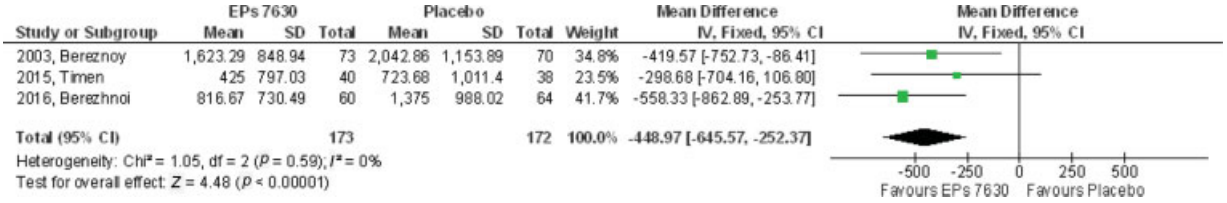

Fig. 2 Cumulative use of paracetamol (mg). CI, confidence interval; SD, standard deviation.

effect. Moreover, significant advantages of EPs 7630 over placebo were also observed for each individual clinical trial.

Discussion

The avoidance of mostly unnecessary antipyresis is an important clinical objective in the treatment of viral acute respiratory infections, particularly in children. The present meta-analysis aimed at investigating whether symptomatic treatment with EPs 7630 may reduce coadministration of paracetamol in children with ATP, an issue which has not been subject to an in-depth analysis so far.

The present meta-analysis included all double-blind, randomized, placebo-controlled, clinical trials in which the administration of EPs 7630 to children suffering from ATP was investigated and which were published by the end of November 2018. ATP is a commonly used term for acute pharyngitis with simultaneously affected tonsils (acute tonsillitis),[42] whereas it should be noted that the current International Classification of Disease-10th Revision (ICD-10) classification refers to acute pharyngitis and acute tonsillitis as separate diagnostic categories. By presenting a deeper insight into results from clinical trials investigating treatment with EPs 7630 in children with ATP, this meta-analysis adds to the evidence from previously published systematic reviews which included studies in several acute respiratory tract infections.[22,28,29,43] The present results of pooled data from ATP trials only demonstrate that EPs 7630 reduces paracetamol use in children suffering from ATP and additionally show that the use of EPs 7630, in the indication ATP, significantly reduces the percentage of children still unable to go to school after a week's treatment. The results of our meta-analysis are therefore in line with those of a meta-analysis reported earlier, in which data of 523 children from six randomized, placebo-controlled trials investigating EPs 7630 in ATP (three trials) or acute bronchitis (three trials) were analyzed with regard to paracetamol use.[43] However, as the six trials included in this former meta-analysis used different prescriptions for paracetamol dosing and, therefore, size effects could not be excluded, the authors had to use a standardized effect size measure for the analysis. In the present investigation, all eligible trials used identical prescriptions for paracetamol dosing and, therefore, cumulative paracetamol use could be analyzed in the original scale, which is a more tangible effect size measure. Moreover, the present results refer exclusively to ATP and, in this way, add to medical knowledge in this disease.

In all studies included into our meta-analysis, additional intake of paracetamol was allowed in case of fever $\geq$38.5°C. Fever is a closely regulated increase in body temperature that has evolved as an adaptive host response to infection.[8,9,12] In vitro experiments suggest that fever plays a key role in reducing the virulence and increasing the clearance of microorganisms, as well as in stimulating the immune response by supporting the activation and proliferation of lymphocytes,[9,12] by enhancing the phagocytic potential of dendritic cells, and by augmenting interferon-α production in response to viral infection.[11] There is no indication shown in clinical trials that antipyretic treatment may reduce the duration of a febrile disease,[10] and there is no evidence that children with fever are at an increased risk of adverse outcomes.[8]

Since EPs 7630 has no known direct antipyretic effect, the fact that the cumulative paracetamol dose was systematically lower in the EPs 7630 group than in the placebo group indicates that children treated with the herbal product were less febrile, not as a result of the antipyretic treatment but because of a more favorable course of the infection. The results suggest that the clinical picture of the children was improved by treatment with EPs 7630 in such a way that parents administered their children paracetamol less frequently and that the children were able to return to school earlier.

The interpretation is consistent with preclinical data regarding the assumed mechanism of action of EPs 7630; in vitro and in vivo experiments showed that the extract

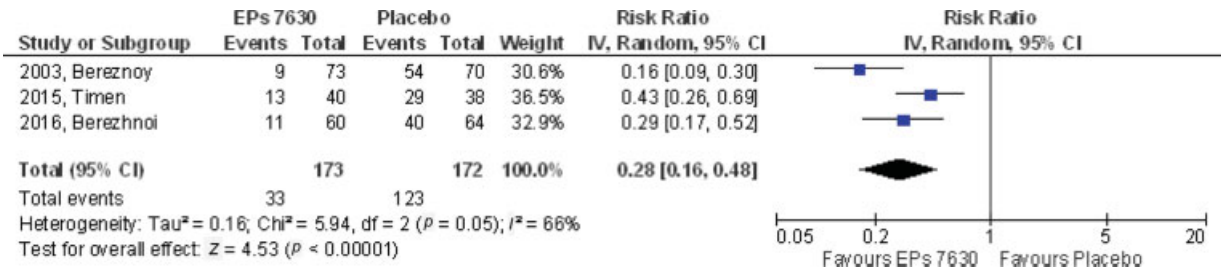

Fig. 3 Inability to attend school. Number of children who were unable to go to school due to acute tonsillopharyngitis at day 6 after start of treatment. CI, confidence interval.

activates the host immune response through the release of tumor necrosis factor-α and nitric oxides, the stimulation of interferon-β, and an increase in natural killer cell activity.[16–19] A therapeutic effect is achieved by preventing viruses released from host cells after one life cycle from entering new host cells for the next life cycle.[21] In addition to its antiviral activity, EPs 7630 also has an antibacterial effect, for example, by inhibiting the adhesion of GAS to human epithelial cells.[44–46] It can therefore be concluded that children benefitted from treatment with EPs 7630 toward a more favorable course of the disease because of its pharmacological mode of action, such as alleviation of symptoms of cytokine-induced sickness behavior, and antiviral activity as shown in vivo.[21,47] These results clearly demonstrate the beneficial effects of treatment with EPs 7630, especially in children with ATP and the resulting reduction in paracetamol use. This in turn leads to a reduction of the risk of rare but potentially harmful side effects and unintentional overdose in children.

This interpretation is also in accordance with the observation from the single trials that children exposed to EPs 7630 recovered from ATP-associated symptoms more rapidly.

A methodological weakness of our study may lie in the comparatively small number of patients available for meta-analysis. It is mentionable, however, that the sample size of each clinical trial had been planned according to statistical considerations and proved to be sufficient for demonstrating the superiority of the herbal extract over placebo for the predefined primary outcome measure. Especially in a vulnerable patient population, such as children, it can also hardly be justified from an ethical point of view to include more patients into a placebo-controlled, clinical trial than the minimum number required to provide an acceptable statistical power for achieving the primary trial endpoint.

Conclusion

Our results demonstrate that children treated with EPs 7630 for non-GAS ATP required less paracetamol comedication and were able to return to school earlier than those exposed to placebo. These results thus support and extend findings from randomized, placebo-controlled trials which confirm that EPs 7630 reduces the severity and duration of ATP-associated symptoms in a pediatric population. Considering the observed reduction in paracetamol use on one hand and the earlier return to school on the other hand, our results can be interpreted in a way that, under EPs 7630 treatment, children were less febrile, not as a result of antipyretic treatment but because of a more favorable course of their infection.

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Conflict of Interest
G.S. has received honoraria from Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany. P.F. and T.R. are employees of Dr. Willmar Schwabe GmbH & Co. KG. W.L. has received honoraria from Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.

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