



Impact of acupuncture on antihistamine use in patients suffering seasonal allergic rhinitis: secondary analysis of results from a randomised controlled trial

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ABSTRACT

Background Seasonal allergic rhinitis (SAR) is a common disease that has detrimental effects on the quality of life (QoL) of affected individuals. Approximately 18% of patients try to alleviate their symptoms through acupuncture. The ACUSAR (ACUpuncture in Seasonal Allergic Rhinitis) study (ClinicalTrials.gov registration no. NCT00610584) assessed the impact of acupuncture on SAR, showing significant improvements in rhinitis-specific QoL (RQoL) and in rescue medication (RM) use.

Objective A secondary analysis of SAR patients' use of antihistamine.

Methods Patients were randomised into three study groups: acupuncture plus RM, sham acupuncture plus RM, and RM alone. The patients documented their medication use before and during the intervention period (8 weeks). The main outcome was the number of days with antihistamine use. Statistical analyses were conducted using parametric and non-parametric tests. The robustness of the results was tested by sensitivity analyses using non-parametric bootstrapping.

Results The data from 414 patients were analysed. The acupuncture group used antihistamines significantly less often compared with the other groups (acupuncture vs sham acupuncture: mean difference -4.49 days, $p=0.01$; acupuncture vs RM: mean difference -9.15 days, $p<0.001$). Approximately 38% of the acupuncture group did not use any antihistamine in contrast to only 16% in the RM group. The pre-post comparison suggested that the acupuncture patients did not need to increase the days of antihistamine use to alleviate their symptoms, unlike the other groups.

Conclusions Acupuncture appeared to significantly reduce the number of days of antihistamine use while improving RQoL and SAR symptoms; it can therefore be considered a valuable, additional treatment option for patients with SAR.

Trial registration number NCT00610584; Post-results.

INTRODUCTION

Allergic rhinitis (AR) is a common chronic disorder that has a considerable social and economic impact on the healthcare system, society, and the individual patient. The disease is triggered by allergens that set off various symptoms such as rhinorrhoea, sneezing, nasal obstruction and itching.¹ It restricts daily activities by disturbing patients' sleep and causing headaches and poor concentration. Therefore, AR lowers patients' quality of life (QoL).² Approximately 23% of Europe's adult population is affected by AR.³ Clinical guidelines strongly recommend second-generation oral antihistamines as a symptomatic treatment for AR.⁴ In Germany, one of the most prescribed antihistamines is the low-cost generic drug cetirizine.⁵ Antihistamines commonly cause side effects such as fatigue, dizziness, headache, sleepiness and sore throat.⁶

Many patients try to alleviate symptoms through complementary and alternative medicine (CAM). An estimated 18% of the seasonal AR (SAR) patients in Germany have used acupuncture treatments for their condition.⁷ The ACUSAR trial (ACUpuncture in Seasonal Allergic Rhinitis) conducted by our research group assessed the effects of acupuncture as a treatment for SAR. The three-armed, randomised controlled trial compared acupuncture with sham acupuncture and rescue medication (RM). The results showed significant changes in favour of acupuncture treatment, including improvements in RQoL and SAR symptom scores. The use of medication



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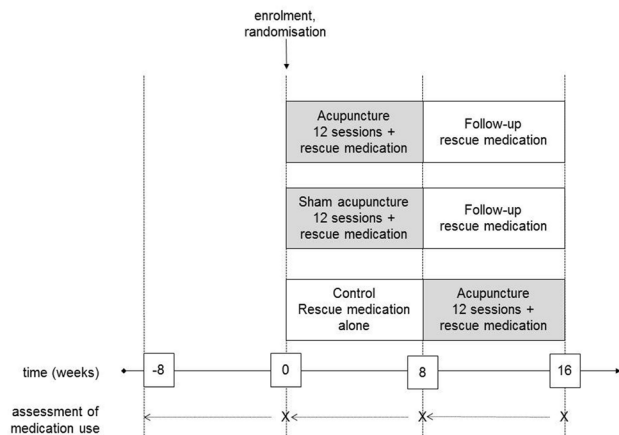


Figure 1 Study design and time points for the outcome measurements.

was assessed by a rescue medication score (RMS). The results indicated a decreased amount of antihistamines used by patients who were treated by acupuncture compared with those treated by sham acupuncture and RM alone.⁸

Detailed patterns of antihistamine use have not yet been analysed in the ACUSAR study. The goal of this secondary analysis was to investigate the influence of acupuncture on the use of antihistamines in patients with SAR. In contrast to previous analyses of the ACUSAR trial, we focused on the duration and not on the amount of medication used. It was important for us to investigate the time dimension because antihistamines can have a negative influence on patients' daily life and activities due to side effects.

METHODS

Study design

The underlying data of the analyses originates from the ACUSAR trial, a three-armed, randomised, controlled, multicentre study conducted in 2008 and 2009 in Germany. Further details of the study protocol have been published previously.⁹ The primary outcomes were RQoL and medication use, in an acupuncture group (acupuncture plus RM), a sham acupuncture group (penetrating sham acupuncture plus RM), and an RM group (waiting-list control group receiving RM alone). The study was conducted in accordance with the Declaration of Helsinki Good Clinical Practice guidelines and involved an external audit. Written informed consent was provided by all study participants. The study protocol was authorised by the ethics review committee of the Charité University Hospital Berlin.

Patients

The inclusion criteria were age from 16 to 45 years, a medical diagnosis of moderate to severe SAR lasting for at least 2 years, and no contraindications to cetirizine. The exclusion criteria were perennial AR, allergic asthma, moderate to severe atopic dermatitis,

autoimmune disorders, severe chronic inflammatory diseases, a history of anaphylactic reactions, hypersensitivity to cetirizine or related drugs, specific immunotherapy during the last 3 years or planned in the next 2 years, pregnancy or breastfeeding, previous acupuncture treatment for SAR, and any further use of CAM.

Randomisation and interventions

The patients were asked to participate in the study at the beginning of the pollen season and after the appearance of their first SAR symptoms. Then they were randomised using a 2:1:1 allocation ratio (acupuncture, sham acupuncture, RM). Randomisation was carried out through a centralised telephone randomisation procedure. The participants who received acupuncture and sham acupuncture from the beginning of the study were blinded to the treatment allocation for the entire study. Throughout the first 8 weeks, the patients received the study interventions according to their group allocations. The acupuncture group received 12 sessions of semi-standardised acupuncture and the sham group received 12 sham acupuncture sessions by trained physicians with additional extensive acupuncture training. The patients of the acupuncture group were treated at four obligatory basic Chinese medicine acupuncture points (LI4, LI11, LI20 bilaterally and *Yintang*), at least three of eight facultative basic points (*Bitong*, GB20, LR3, LU7, ST36, SP6, TE17 or BL13) and at least three additional points. Further details are described in the study protocol.⁹ The RM group received no acupuncture in the first 8 weeks. Afterwards, all groups received the other treatment option (weeks 8 to 16): the RM group received 12 acupuncture sessions, and the other two groups were followed-up without further interventions, but they could use RM (figure 1). When needed, all patients were allowed to take up to 20 mg of the second-generation oral antihistamine per day as RM. The use of cetirizine was strongly recommended. If the symptoms of SAR were not manageable by antihistamine treatment, the use of an oral corticosteroid was permitted (methylprednisolone), but no other anti-allergic medications were allowed. The drugs were provided by the study centres free of charge.

Data collection and outcome definitions

At baseline, week 8 and week 16, the patients were asked to provide information about their use of SAR-related medication during the past 8 weeks by means of self-reported questionnaires (the name of the drug, days of use, pharmaceutical form, dosage and manufacturer). Socioeconomic status (SES) was assessed according to Winkler.¹⁰

Documented drugs were categorised into groups of active substances for the respiratory tract by the Anatomic Therapeutic Chemical (ATC) classification system. The ATC classification divides active substances according to the human organs and systems

they affect as well as their chemical, pharmaceutical and therapeutic properties.¹¹

Statistical analyses

Baseline characteristics were described by arithmetical means and standard deviations (SD), respectively. To describe the use of medication at baseline and during the intervention period in detail, the means for the days of medication use were calculated for the different groups of active substances according to the ATC classification, first for all patients and second for patients who actually used medication (actual users). This approach was intended to demonstrate the specific use of the different medications at the times of measurement.

The mean number of days of antihistamine use at baseline and during the intervention period (baseline until week 8) were compared between the acupuncture and the sham acupuncture groups as well as between the acupuncture and RM groups. A subgroup analysis for sex was similarly conducted. The mean differences in antihistamine use by the groups and subgroups were analysed by Student's t-test with 95% confidence intervals (CI). Although the days of antihistamine use were not normally distributed, we decided to analyse

the data parametrically: first, because we chose to calculate the mean days of antihistamine use rather than median days, since high or extreme values should be included in the results and in our interpretations; and second, because the sample sizes of each group can be considered sufficient for the t-test to be valid. Nevertheless, we tested the robustness of the group comparisons by sensitivity analyses. To test the mean differences, we used non-parametric bootstrapping.¹² Therefore, the original sample was replicated 1000 times (draw and return) to obtain 1000 means for the days of antihistamine use for all groups and their mean differences. To verify the t-test-based p values of the group comparisons, we conducted a non-parametric Mann-Whitney-U test.

The days of antihistamine use for each patient were categorised into no antihistamine use (non-users), 0 to ≤15 days, 15 to ≤30 days, 30 to ≤45 days, and >45 days. The proportion of patients belonging to each category was calculated. Additionally, a χ^2 test was conducted to analyse the differences between the treatment groups in the 'no antihistamine use' (d=0) category.

Table 1 Baseline characteristics.

Patient characteristics	Acupuncture (n=210)		Sham acupuncture (n=98)		Rescue medication (n=106)		Total (n=414)	
Age, mean, years (SD)	33.4	(7.5)	33.0	(8.3)	32.2	(8.1)	33.0	(7.8)
Sex, female, No. (%)	130	(62)	63	(64)	55	(52)	248	(60)
Socioeconomic status, No. (%)								
Lower	26	12	15	15	14	13	55	13
Middle	91	(43)	41	(42)	39	(37)	171	(41)
Upper	93	(44)	42	(43)	53	(50)	188	(45)
Recruitment region, No. (%)								
Bavaria	71	(34)	35	(36)	39	(37)	145	(35)
Berlin/Brandenburg	121	(58)	54	(55)	58	(55)	233	(56)
North Rhine-Westphalia	4	2	2	2	2	2	8	2
Saxony	14	7	7	7	7	7	28	7
RQoL, mean (SD)	2.7	(1.2)	2.3	(1.1)	2.5	(1.2)	2.5	(1.2)
VAS score, mean (SD)	48.9	(26.5)	43.6	(26.1)	44.2	(26.5)	46.5	(26.5)
Days of use relative to all patients, mean (SD)								
Nasal preparations	4.3	12	2.7	(10.1)	1.8	(5.1)	3.3	(10.2)
Anti-obstructive drugs	1.6	(5.8)	1.0	(3.6)	0.9	(3.1)	1.3	(4.8)
Antihistamines	9.8	(16.2)	10.1	(16.2)	8.3	(13.7)	9.5	(15.6)
Actual users, No. (%)								
Nasal preparations	52	(25)	17	17	18	17	87	21
Anti-obstructive drugs	27	13	12	12	10	9	49	12
Antihistamines	120	(57)	50	(51)	52	(49)	222	(54)
Days of use relative to actual users, mean (SD)								
Nasal preparations	17.4	(18.9)	15.6	(20.2)	10.8	(7.7)	15.7	(17.5)
Anti-obstructive drugs	12.8	(11.1)	8.1	(7.3)	9.1	(5.6)	10.9	(9.5)
Antihistamines	17.1	(18.3)	19.8	(18.1)	16.9	(15.4)	17.6	(17.6)

RQoL, rhinitis-specific quality of life; SES, socioeconomic status; VAS, visual analogue scale.

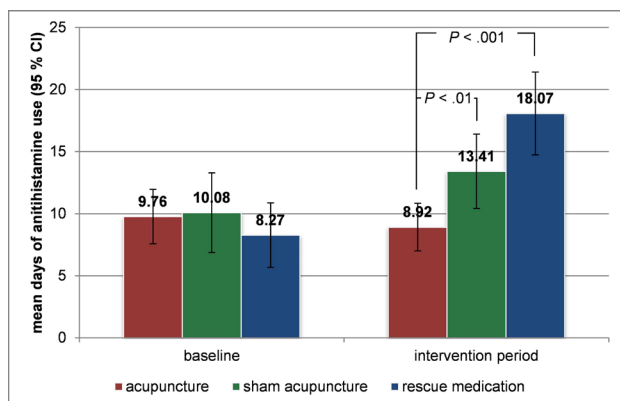


Figure 2 Days of antihistamine use by the groups at baseline and during the intervention period.

For the pre-post comparison, the changes in the days of antihistamine use from baseline to 8 weeks were calculated for each patient, and analysed as mean and 95% CI; p values were calculated by the Wilcoxon test (paired sample).

We did not analyse data from the follow-up period (week 8 until week 16) because of the suspected offset of the pollen season and the waiting list design.

The significance level was defined as $\alpha=0.05$. No corrections were applied for multiple testing since this was only an exploratory analysis. The analyses were performed by PASW statistics version 22.0.0.1 (SPSS Inc, Chicago, Illinois, USA). Bootstrap analyses were conducted in MS Excel 2010 (Microsoft Inc, Redmond, Washington, USA).

RESULTS

Baseline characteristics

A total of 1588 SAR patients were initially screened for eligibility at the beginning of the pollen season between March and May 2008 and 2009. Five hundred and ninety-nine patients were considered suitable for the study, and 422 were randomly assigned to the three arms of the study. Complete baseline information was available for 414 patients (acupuncture $n=210$, sham acupuncture $n=98$, and RM $n=106$).

The mean (SD) age was 33 (7.8) years. The scores for rhinitis-specific quality of life (RQoL score) and SAR symptoms (visual analogue scale (VAS) score) did not differ between the groups. Further baseline characteristics were comparable between the three groups. The proportion of female participants was slightly higher

compared with men in all treatment groups. According to the ATC classification, three main groups of active substances arose from the data: nasal preparations (eg, prednisolone, cromoglicic acid), anti-obstructive drugs (eg, salbutamol, budesonide), and antihistamines (eg, cetirizine). There was no relevant difference in the mean days of antihistamine use between the treatment groups at baseline (table 1).

Baseline to 8 weeks

During the intervention period, the acupuncture group used antihistamines on significantly fewer days compared with the sham acupuncture group (-4.49 days, 95% CI -8.00 to -0.98 ; $p=0.01$) and the RM group (-9.15 days, -13.03 to -5.28 ; $p<0.001$) (figure 2).

The results of the sex-specific subgroup analysis for the intervention period were comparable to the results of the main analysis. Mean differences of -3.37 days (95% CI -7.80 to 1.06 ; $p=0.14$) emerged in the comparison of female patients within the acupuncture and sham acupuncture groups, and -9.47 days (95% CI -14.87 to -4.08 ; $p=0.001$) in the acupuncture and RM groups. For male patients, the mean differences were -6.55 days (95% CI -12.38 to -0.72 ; $p=0.03$) for the comparison between the acupuncture and the sham acupuncture groups, and -9.30 days (95% CI -15.06 to -3.53 ; $p=0.002$) between the acupuncture and RM groups.

Table 2 shows the use of antihistamines by group during the intervention period. Considering all acupuncture patients, antihistamines were used for 8.92 days (95% CI 6.99 to 10.85) on average (sham acupuncture 13.41 days, 95% CI 10.37 to 16.45; RM 18.07 days, 95% CI 14.69 to 21.45). Regarding the pre-post comparison (changes in antihistamine use from baseline to week 8), no significant differences emerged in the acupuncture group (mean difference -0.92 days, 95% CI -3.43 to 1.59 ; $p=0.722$). The results for the sham acupuncture group showed slightly increased usage with a mean difference of an additional 4.22 days (95% CI 0.07 to 8.37; $p=0.005$). In contrast, the mean difference in antihistamine use in the RM group increased significantly (mean difference 9.52 days, 95% CI 5.81 to 13.22; $p<0.001$). Only 60% of all acupuncture patients took any antihistamines during the intervention period compared with the sham acupuncture (71%) and RM (82%) groups.

Table 2 Use of antihistamines during the intervention period.

		Acupuncture (n=201)	Sham acupuncture (n=90)	Rescue medication (n=98)
Referring to all patients	Days of use (95% CI)	8.92 (6.99 to 10.85)	13.41 (10.37 to 16.45)	18.07 (14.69 to 21.45)
	Changes from baseline (95% CI)	-0.92 (-3.43 to 1.59)	4.22 (0.07 to 8.37)	9.52 (5.81 to 13.22)
Referring to users	Actual users, No. (%)	121 (60)	64 (71)	80 (82)
	Days of use (95% CI)	14.74 (12.01 to 17.48)	18.86 (15.39 to 22.33)	21.91 (18.35 to 25.47)
	Changes from baseline, days	-2.34	-0.90	5.06

Taking only these patients into account, they used antihistamines for 14.74 days on average (sham acupuncture 13.41 days; RM 18.07 days) (table 2).

Only two patients in the underlying study population used methylprednisolone. The use of nasal preparations and drugs for obstructive respiratory disorders decreased from baseline to week 8. Similarly across the treatment groups, 5.7% of patients continued taking nasal preparations and 2.6% of patients continued taking anti-obstructive drugs during the intervention period. Consequently, only the days of antihistamine use (mostly cetirizine) were analysed.

Medication use categories

The proportion of patients in each category for the number of days on which antihistamines were used was balanced between all groups at baseline. During the intervention period, 37.6% of acupuncture patients did not use antihistamines (sham acupuncture 26.5%, RM 16.0%). Compared with non-users, the differences between the acupuncture and the RM groups were significant ($p < 0.001$), but not between the acupuncture and sham acupuncture groups ($p = 0.08$) (figure 3).

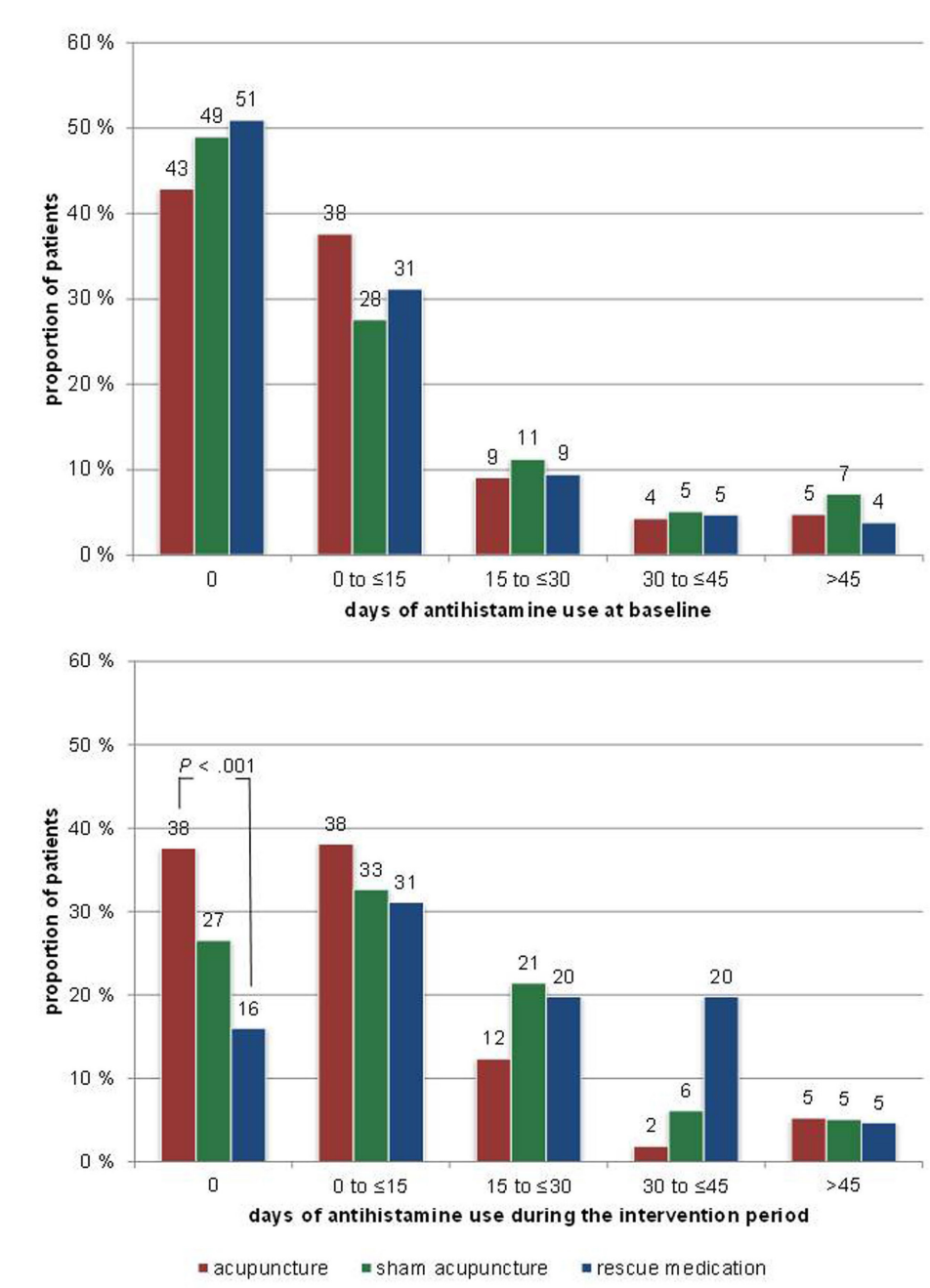


Figure 3 Proportion of patients in various categories for the days of antihistamine use at baseline and during the intervention period for all groups.

Sensitivity analyses

The mean differences in days of antihistamine use between the acupuncture and sham acupuncture groups during the intervention period (mean difference bootstrap -3.83 days, 95% CI -3.94 to -3.72) and between the acupuncture and the RM groups (mean difference bootstrap -8.08 days, 95% CI -8.20 to -7.96) were slightly smaller with the non-parametric bootstrapping approach compared with the main analysis.

The group comparison at baseline and during the intervention period was verified by the conservative non-parametric Mann-Whitney-U test because days of use were not normally distributed, with similar p values compared with the Student's t-test. The groups did not differ at baseline (acupuncture vs sham acupuncture $p=0.64$, and acupuncture vs RM $p=0.32$), but they differed after the intervention (acupuncture vs sham acupuncture $p=0.003$, and acupuncture vs RM $p<0.001$).

DISCUSSION

In the ACUSAR trial, 8 weeks of acupuncture led to significantly fewer days of antihistamine use in patients with SAR compared with sham acupuncture and RM alone. From the onset to the peak of the pollen season, patients treated by acupuncture did not need to increase the number of days of antihistamine use to alleviate their symptoms in contrast to patients who used RM alone. In addition, fewer patients in the acupuncture group started using antihistamines during the intervention period compared with both other groups. These findings support the result of the primary report that showed improvements in RQoL and RMS. Therefore, the RMS values and the days of antihistamine use were reduced markedly in SAR patients who were treated with acupuncture. At the same time, SAR symptoms decreased significantly in the acupuncture group compared with the other study groups. From this point of view, acupuncture treatment was more effective than the symptomatic drug intervention.

One explanation for the findings could be the treatment effect expectation of the patients receiving acupuncture. They may have been more likely to abstain from medication because they believed that the treatment would have an effect on their health. If this explanation were true, there would likely have been significant differences between the sham acupuncture and the RM groups after 8 weeks of treatment since the patients were blinded to the real and the sham acupuncture treatments. This was not verified by the results of our analyses.

Acupuncture treatments provided by physicians are relatively safe. Common side effects are bleeding and haematoma due to lesions in the small vessels caused by the acupuncture needles.¹³ In contrast, antihistamines like cetirizine commonly cause fatigue, dizziness, headaches, sleepiness and sore throat.⁶ They reduce patients' QoL and affect daily life and

activities. Therefore, antihistamine use has negative consequences for the patient and for society.¹⁴ Clinical guidelines for the management of AR strongly recommend antihistamines for treatment, and acupuncture is listed as an alternative or supplementary option for patients who are interested in a non-pharmacological therapy.⁴ The results encourage consideration of the need for a stronger position of acupuncture in clinical guidelines.

From an economic perspective, acupuncture does not seem to be a cost-effective treatment for SAR. This is partly because antihistamines are inexpensive generic drugs whereas acupuncture is a resource-consuming treatment.¹⁵ The above-mentioned losses in productivity are difficult to estimate and are therefore scarcely considered in economic evaluations.¹⁶ In addition, the lack of appropriate methods prevents an evaluation of complementary and integrative medicine outcomes beyond health, such as the benefits that patients achieve from the treatment process itself.¹⁷ Therefore, from an economical point of view, it is not clear how relevant the findings are.

We are aware of four clinical trials^{18–21} that similarly assessed the amount of medication used based on RM scores by comparing acupuncture with sham acupuncture. None of the trials found significant differences in RM scores. The latest study showed a trend in favour of acupuncture treatment reducing RM intake, but it was not significant.¹⁸ However, none of the studies analysed the number of days of medication use. To our knowledge, this is the first investigation on this topic.

Important strengths regarding the study design are the large number of participants, the three-armed randomised design, the quality of the dataset, and the pragmatic setting in the outpatient practices of participating physicians.¹⁵ Additionally, we conducted sensitivity analyses that supported the robustness of the results.

The baseline characteristics showed slight differences relative to the use of nasal preparations and antihistamines between the three groups. More patients in the acupuncture group used these drugs at baseline. We decided not to adjust for the differences since they were less favourable for acupuncture treatment.

Several limitations must be considered in the study design. The SAR patients were mainly recruited through the media, which may not have generated a representative study population. We presume that patients who are interested in acupuncture treatment may be prejudiced in favour of it and are more likely to take part. It was not possible to blind the RM group. Unblinding was improbable, but it cannot be ruled out in the acupuncture and sham acupuncture groups.⁸ Another important limitation is the fact that no conclusions can be drawn regarding the second time period (8 to 16 weeks) due to the suspected offset of the pollen season and the waiting list design. Furthermore, patients took cetirizine as an RM because it

was recommended and provided by the study centres as the RM standard in the ACUSAR trial. In real-life conditions, patients may arguably have used a greater variety of anti-allergic medications. This may affect the generalisability of the results.

In conclusion, acupuncture significantly lowered the days of antihistamine intake in patients with SAR compared with a sham acupuncture group and a group that used RM alone. When the positive effects of acupuncture on symptoms and disease-specific quality of life are taken into account, it can be considered a valuable, additional treatment option for SAR patients with the potential to reduce medication-related side effects.

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Contributors DA conceived and designed the analysis (with support from TR, BB and MO), analysed and interpreted the data, and wrote the first draft of the manuscript. TR supervised the analysis. LG provided statistical support. SB addressed the quality assurance of data entry and data safety. All authors were involved in the critical revision of the manuscript and approved the final version accepted for publication.

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Competing interests BB has received travel expenses, accommodation and free congress registration from acupuncture societies. The other authors have nothing to declare.

Patient consent Obtained.

Ethics approval Ethics review committee of the Charité University Hospital, Berlin.

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