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Anthroposophic vs. conventional therapy of acute respiratory and ear infections: a prospective outcomes study

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Anthroposophische vs. konventionelle Therapie bei akuten Ohr- und Atemwegsinfekten: eine prospektive Outcome-Studie

Zusammenfassung. *Hintergrund:* Akute Atemwegs- und Ohrenbeschwerden werden oft mit Antibiotika behandelt. In der anthroposophischen Medizin werden solche Beschwerden überwiegend mit anthroposophischen Arzneimitteln behandelt.

Fragestellung: Vergleich von anthroposophischer und schulmedizinischer Behandlung akuter Atemwegs- und Ohrenbeschwerden hinsichtlich Krankheitsverlauf, Arzneimittelverbrauch und -sicherheit sowie Patientenzufriedenheit.

Design: Prospektiver nicht-randomisierter Outcomes-Vergleich von Patienten, die durch Selbstselektion zu anthroposophischer oder schulmedizinischer Behandlung unter den Bedingungen der Alltagsrealität kamen.

Setting: 29 Hausarztpraxen in Deutschland, Großbritannien, Niederlande, Österreich, USA.

Teilnehmer und Behandlung: 1016 konsekutiv aufgenommene Patienten im Alter ≥ 1 Monat, die einen anthroposophischen (n = 715 A-Patienten) oder schulmedizinischen Arzt (n = 301 S-Patienten) wegen akuter (≤ 7 Tage) Beschwerden aufsuchen: Husten, Rhinorrhö, Hals-, Nebenhöhlen- oder Ohrenschmerzen. Behandlung nach Ermessen des Arztes.

Primärer Zielparameter: Patientenangaben über Behandlungserfolg (beschwerdefrei / deutlich gebessert / leicht bis mäßig gebessert / unverändert / verschlechtert) nach 14 Tagen.

Ergebnisse: Die häufigsten Hauptbeschwerden waren Husten (39,9% der A-Patienten bzw. 33,9% der S-Patienten, p = 0,0772), Halsschmerzen (26,3% bzw. 23,3%, p = 0,3436) und Ohrenschmerzen (20,0% bzw. 18,9%, p = 0,7302). Die Ausprägung der Hauptbeschwerde war bei Studienaufnahme stark oder sehr stark bei 60,5% der A-Patienten und 53,3% der S-Patienten (p = 0,0444); die Ausprägung (0–4) beschwerdebezogener Symptome betrug im Durchschnitt 1,3 ± 0,7 bzw. 1,2 ± 0,6 (p = 0,5197). Während des 28-tägigen Follow-ups wurden Antibiotika an 5,5% der A-Patienten und 33,6% der S-Patienten verschrieben (p < 0,0001); anthroposophische Arzneimittel wurden allen A-Patienten und keinem S-Patienten verschrieben.

Eine Besserung trat innerhalb von 24 Stunden bei 30,9% (221/715) der A-Patienten und 16,6% (50/301) der S-Patienten auf (p < 0,0001), eine Besserung innerhalb von 3 Tagen bei 73,1% bzw. 57,1% (p < 0,0001). Der Anteil beschwerdefreier oder deutlich gebesserter Patienten betrug nach 7 Tagen 77,1% in der A-Gruppe und 66,1% in der S-Gruppe (p = 0,0004), nach 14 Tagen 89,7% bzw. 84,4% (p = 0,0198). Die Anteile beschwerdefreier Patienten betrugen nach 7 Tagen 30,5% bzw. 23,3% (p < 0,0001), nach 14 Tagen 64,2% bzw. 49,5% (p < 0,0001). Sehr zufrieden mit ihrem Arzt waren 69,9% der A-Patienten und 60,5% der S-Patienten (p = 0,0043); 95,7% bzw. 83,4% würden sich für dieselbe Behandlung ihrer Hauptbeschwerde wieder entscheiden (p < 0,0001). Nach Adjustierung für Land, Geschlecht, Alter, Hauptbeschwerde, Dauer der Hauptbeschwerde, Auftreten der Hauptbeschwerde im letzten Jahr sowie Ausprägung der Krankheitssymptomatik bei Studienaufnahme zeigten Odds Ratios eine Überlegenheit der A-Gruppe hinsichtlich aller dieser Ergebnisse. Unerwünschte Arzneimittel-

wirkungen wurden von 2,7% der A-Patienten und 6,0% der S-Patienten berichtet (p = 0,0157).

Schlussfolgerung: Im Vergleich zur schulmedizinischen Behandlung erzielte die anthroposophische Behandlung hausärztlicher Patienten mit akuten Atemwegs- oder Ohrenbeschwerden günstigere Krankheitsverläufe, niedrigere Antibiotika-Verschreibungsraten und weniger Arzneimittelnebenwirkungen bei höherer Patientenzufriedenheit.

Summary. *Context:* Acute respiratory and ear symptoms are frequently treated with antibiotics. Anthroposophic treatment of these symptoms relies primarily on anthroposophic medications.

Objective: To compare anthroposophic treatment to conventional treatment of acute respiratory and ear symptoms regarding clinical outcome, medication use and safety, and patient satisfaction.

Design: Prospective, non-randomised comparison of outcomes in patients self-selected to anthroposophic or conventional therapy under real-world conditions.

Setting: 29 primary care practices in Austria, Germany, Netherlands, UK, and USA.

Participants and therapy: 1016 consecutive outpatients aged ≥ 1 month, consulting an anthroposophic (n = 715 A-patients) or conventional physician (n = 301 C-patients) with a chief complaint of acute (≤ 7 days) sore throat, ear pain, sinus pain, runny nose or cough. Patients were treated according to the physician's discretion.

Primary outcome: Patients' self-report of treatment outcome (complete recovery / major improvement / slight to moderate improvement / no change / deterioration) at Day 14.

Results: Most common chief complaints were cough (39.9% of A-patients vs. 33.9% of C-patients, p = 0.0772), sore throat (26.3% vs. 23.3%, p = 0.3436), and ear pain (20.0% vs. 18.9%, p = 0.7302). Baseline chief complaint severity was severe or very severe in 60.5% of A-patients and 53.3% of C-patients (p = 0.0444), mean severity (0–4) of complaint-related symptoms was 1.3 ± 0.7 vs. 1.2 ± 0.6 (p = 0.5197). During the 28-day follow-up antibiotics were prescribed to 5.5% of A-patients and 33.6% of C-patients (p < 0.0001), anthroposophic medicines were prescribed to all A-patients and no C-patient.

Outcomes: Improvement within 24 hours occurred in 30.9% (221/715) of A-patients and 16.6% (50/301) of C-patients (p < 0.0001), improvement within 3 days in 73.1% and 57.1% (p < 0.0001). At Day 7 complete recovery or major improvement was reported by 77.1% of A-patients and 66.1% of C-patients (p = 0.0004), at Day 14 by 89.7% and 84.4% (p = 0.0198). Complete recovery rates at Day 7 were 30.5% and 23.3% (p < 0.0001); at Day 14 they were 64.2% and 49.5% (p < 0.0001). 69.9% of A-patients and 60.5% of C-patients were very satisfied with their physician (p = 0.0043); 95.7% and 83.4% would choose the same therapy again for their chief complaint (p < 0.0001). After adjustment for country, gender, age, chief complaint, duration of complaint, previous episode of complaint within last year, and baseline symptom severity, odds ratios favoured the A-group for all these outcomes. Adverse drug reactions were reported in 2.7% of A-patients and 6.0% of C-patients (p = 0.0157).

Conclusion: Compared to conventional treatment, anthroposophic treatment of primary care patients with acute respiratory and ear symptoms had more favourable outcomes, lower antibiotic prescription rates, less adverse drug reactions, and higher patient satisfaction.

Key words: Anthroposophy, anti-bacterial agents, bronchitis, comparative study, otitis media, pharyngitis, respiratory tract infections, sinusitis, tonsillitis.

Introduction

Acute respiratory tract infections (RTI) and *otitis media (AOM)* are very frequent in primary care [1]. Although mostly self-limiting within 1–2 weeks [2–5], the total burden of RTI and AOM due to symptoms and school/work absence is formidable. In the WHO Global Burden of Disease Study, RTI caused 8.5% of Disability Adjusted Life Years worldwide [6].

Most patients seeing a physician for RTI/AOM are prescribed antibiotics [7–12]. This practice is not well-supported by research evidence. Cochrane Reviews of randomised controlled trials in AOM, sinusitis, tonsillitis, common cold, and bronchitis found small or negligible effects of antibiotics, comparable to their side-effect potential [3, 13–16]. Since complications of RTI/AOM are rare in most Western settings [5, 17], antibiotic prophylaxis to prevent complications requires that many patients take antibiotics unnecessarily [3]. Furthermore, antibiotics induce antimicrobial resistance, a major threat to public health [18]. Therefore, antibiotic prescription for RTI/AOM should be reduced [19–23]. Guidelines do not recommend routine use of antibiotics for the common cold or bronchitis [24–28]; for sinusitis only if symptoms are severe or persist [26, 29, 30]. For AOM and streptococcal pharyngitis, various guidelines advise for [26, 31–35] or against [36-39] routine antibiotic use.

Anthroposophic medicine (AM) was founded in the 1920s by Rudolf Steiner and Ita Wegman [40, 41]. AM aims to stimulate the patient's salutogenetic, self-healing capacities [42]. AM is practiced in over 80 countries by licensed physicians with postgraduate AM training. AM treatment of RTI/AOM relies on an array of AM medications, supported by external herbal and hydrotherapeutic applications. Antibiotics are only recommended if strongly needed; fever is not routinely suppressed with analgesics [41–45].

Prospective cohort studies of AM as a whole system [46, 47] and of singular AM medications [48–50] for AOM [46, 48], pharyngitis [47], and bronchitis [49, 50] have demonstrated low antibiotic use without increased complication rates. However, no concurrent comparison with conventional therapy has been undertaken. Because of strong treatment preferences and ethical considerations, randomisation has traditionally been rejected in AM [51]. On the other hand, a non-randomised comparison of patients choosing treatment by anthroposophic or conventional physicians, adjusting for relevant baseline differences, would seem ethically justifiable and feasible. We performed such a study.

Methods

Study design, objective and hypothesis

This is a GCP-conform prospective observational non-randomised comparative outcomes study in a real-world medi-

cal setting. The study was part of a research project on the effectiveness of complementary and alternative therapies in primary care (IIPCOS, International Integrative Primary Care Outcomes Study). The objective of this study (IIPCOS-Anthroposophy) was to compare clinical outcomes, medication use and safety, and satisfaction in patients seeing either anthroposophic or conventional physicians for acute respiratory or ear symptoms, treated according to the physicians' discretion. Treatments were evaluated as global packages, including physician-patient interactions. The hypothesis was that clinical outcomes would not be worse after anthroposophic treatment than after conventional treatment.

Setting, participating physicians, patients

The study was conducted in primary care practices in Austria, Germany, Netherlands, UK, and USA. Participating physicians had ≥ 5 years practice. Anthroposophic physicians (prescribing AM medicines to ≥ 75% of patients with RTI/AOM) were recruited through national AM physicians' associations; conventional physicians (not prescribing AM medicines) were recruited by HomInt research network. Within a one-year period, each physician could enrol up to 100 consecutive outpatients.

Inclusion criteria: (1) age ≥ 1 month, (2) chief complaint of sore throat, ear pain, sinus pain, runny nose or cough, (3) onset of chief complaint within 7 days. *Exclusion criteria*: dementia, schizophrenia, psychosis, spinal cord injury, stroke, renal failure, severe hepatic disease, ongoing immunosuppressive treatment, chemotherapy or radiotherapy; alcohol or drug abuse.

Outcome measures

Primary outcome: response (defined as treatment outcome = complete recovery or major improvement. Treatment outcome categories: complete recovery / major improvement / slight to moderate improvement / no change / deterioration) at Day 14. *Other major outcomes:* first improvement ≤ 24 hours and ≤ 3 days, response at Day 7, complete recovery at Days 7 and 14, patient satisfaction with treatment (very satisfied / satisfied / neutral / dissatisfied / very dissatisfied), patients' choice of same therapy again for chief complaint (yes/no). *Further outcomes:* medicine prescription and use, response and recovery at Day 28, adverse drug reactions, serious adverse events, patient satisfaction with physician, patients' choice of same physician again.

Data collection

On Day 0, physicians documented chief complaint (name, duration, previous episodes within last year, diagnosis, severity: 0 = not present, 4 = very severe), severity (0–4) of complaint-related symptoms (sore throat / ear pain / sinus pain: four predefined complaint-related symptoms; cough: five symptoms; runny nose: seven symptoms), concomitant diseases, patients' willingness to be randomised, and therapies. Patients documented demographics and quality of life (adults: SF-12®; children: KINDL®). On Days 7, 14, and 28, patients were interviewed by telephone about treatment outcome, time to first improvement (number of hours or days), medication use and safety, and patient satisfaction.

Data collection, follow-up interviews, and queries were performed by the Institute for Numerical Statistics (now: Omnicare Clinical Research), Cologne, Germany. Interviewers were not blinded towards the anthroposophic setting; patients were informed about the planned comparison of treatment regimens. Except for patients' Day 0 questionnaire, all items were documented by remote data entry. Patients' responses were not made available to physicians. Physicians were paid € 25 per included patient; patients received no remuneration.

Statistical methods

The study was designed to confirm non-inferiority of the primary outcome (response rate at day 14) after anthroposophic treatment in comparison to conventional treatment. Before the study began, we calculated a sample size (assumed response rate 80% in both groups, equivalence region 5%, alpha = 0.025, beta = 0.20, one-sided test of non-inferiority) of 2 x 1006 evaluable patients, and, allowing for attrition, of 2 x 1200 enrolled patients. In case of superior outcome in the anthroposophy group with 95% confidence interval (95%-CI) for group difference > 0, it was deemed feasible to calculate the p-value associated with a test of superiority and to evaluate whether this is sufficiently small to reject convincingly the hypothesis of no difference [52]. No interim analyses were planned or performed, no specific stopping rules formulated.

For patients with complete recovery on Days 7 or 14, study participation was terminated and last observations were carried forward for analysis of subsequent follow-ups. Follow-up data missing for other reasons were also replaced by last observation carried forward, when available.

Patients fulfilling all eligibility criteria with at least one follow-up interview were included in the analysis. Data analysis (SAS 8.2®, SPSS 11.0®, StatXact 5.0.3®) followed the intention-to-treat principle. Two-tailed Fisher's exact test was used for dichotomous data and two-tailed Mann-Whitney U-test for rank ordered data. Major outcomes were analysed in subgroups pertaining to seven prognostic variables identified by systematic literature search: country, gender, age (< 2 years, 2–5, 6–17, 18–34, 35–64, ≥ 65), chief complaint, duration of chief complaint (0–1 day, > 1–2, > 2–7), previous episode of chief complaint within last year (yes/no), baseline symptom score (mean severity of chief complaint and complaint-related symptoms: 0 – < 1, 1 – < 2, 2 – < 3, 3 – 4). Multiple logistic regression was conducted to adjust for all seven variables. Final subgroup and adjusted analyses differed from planned analyses in two aspects: Two age subgroups (6–11, 12–17 years) were grouped together because of low sample size; one prognostic variable (diagnosis of chief complaint) was not included because of redundancy with the chief complaint variable.

Quality assurance, adherence to regulations

The study was approved by local ethics committees, conducted according to the Helsinki Declaration, GCP guidelines, and legal requirements, and reported according to guidelines for reporting non-randomised studies [53, 54]. Written informed consent was obtained from all patients before study entry.

Results

Participating physicians

43 physicians (27 anthroposophic "A-physicians" + 16 conventional "C-physicians") consented to participate, 37 physicians (26 + 11) enrolled patients. 36 physicians (26 + 10) had evaluable patients, these physicians were located in Austria (3 + 3), Germany (7 + 3), NL (6 + 2), UK (2 + 2), and US (8 + 0) in 29 different practices in 23 different municipalities. 83% (20/26) of A-physicians and 80% (8/10) of C-physicians were men. Physi-

cians' qualifications were: general practitioners (19 A-physicians + 7 C-physicians), internists (3 + 2), paediatricians (4 + 0), and otolaryngologist (0 + 1).

Patient recruitment and follow-up

From 21 April 1999 to 30 March 2000 a total of 1171 patients were enrolled. Last follow-up interview was performed 26 April 2000. 1016 patients were evaluable, 155 patients had no evaluable follow-up data and were excluded from analysis:

- 99 patients (98 A-patients + 1 C-patient) from US were excluded because one telephone interviewer, responsible for all interviews with US patients up till 13 Feb 2000, had not performed interviews according to protocol. Since only one C-physician in US had enrolled patients (only one), these exclusions mainly affected A-patients.
- 56 patients (40 A-patients + 16 C-patients) were excluded because no follow-up interviews had been performed. Reasons: technical or practical (35 + 14), patient refusal to participate (5 + 2).

Comparing excluded and evaluable patients in each group, baseline symptom score (0–4) differed significantly in the A-group (mean 1.0 ± 0.6 vs. 1.3 ± 0.7, $p < 0.0001$) but not in the C-group (1.3 ± 0.4 vs. 1.2 ± 0.6, $p = 0.4205$).

For the 1016 (715 + 301) evaluable patients, altogether 2152 (1468 + 684) follow-up interviews were scheduled on Days 7–28. For 219 interviews (151 + 68) data are missing. Reasons: patients unreachable by telephone (79 + 37 interviews), other practical/technical reasons, e. g. remote data entry failure (71 + 24), patient refusal to be interviewed (1 + 7). Percentages of missing data for each follow-up (Fig. 1) did not differ significantly between A- and C-groups.

For administrative reasons, patients' documentation of socio-demographics (race, smoking, household size and income), confidence in therapy, and quality of life at baseline was unavailable for 19.7% (141/715) of A-patients and 12.3% (37/301) of C-patients ($p = 0.0049$).

Screening data were available from 19/26 A-physicians and 0/10 C-physicians. The 19 A-physicians had enrolled 95.0% (679/715) of evaluable A-patients. 878 A-patients were screened but not enrolled, 111 of which refused to participate; 306 did not fulfil all eligibility criteria. 461 (100%) screened A-patients fulfilled all eligibility criteria (NE-A-patients); reasons for non-enrolment were: physician too busy (68.1%), practical/technical (12.1%), ongoing therapy for chief complaint (2.0%), spe-

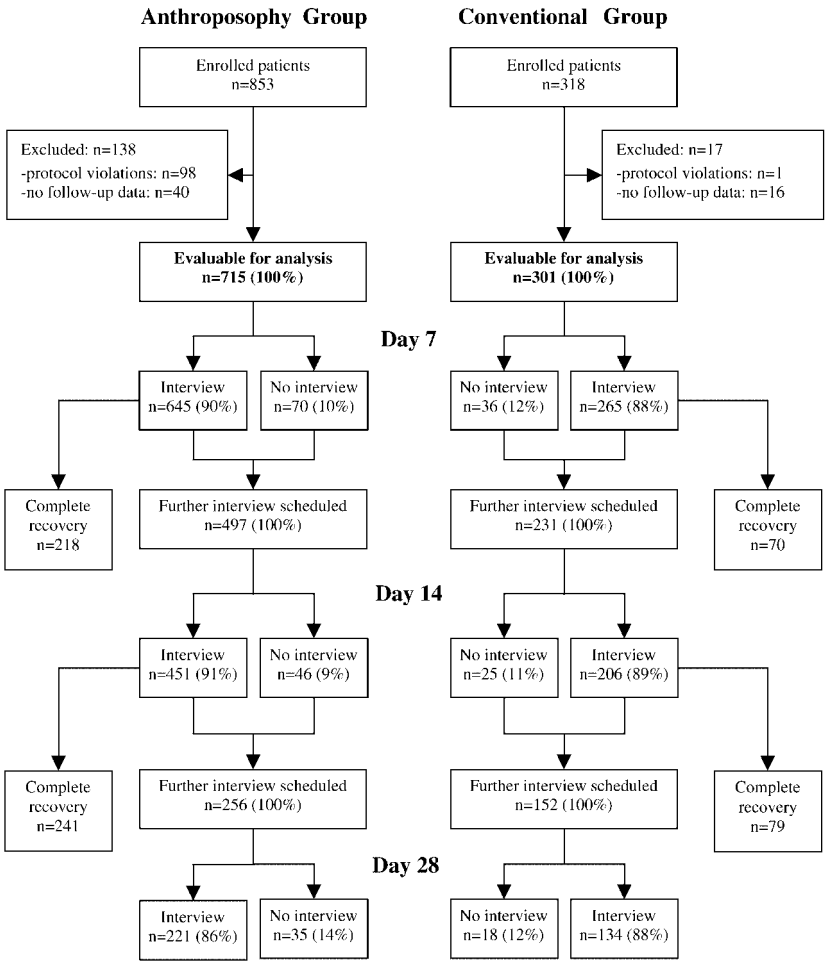

Fig. 1. Patient recruitment and follow-up telephone interviews. All evaluable patients had at least one interview

Table 1. Demographics

	Anthroposophy group (N = 715)		Conventional group (N = 301)		
	N	%	N	%	
Country					
Austria	101	14.1%	57	18.9%	n. s.
Germany	362	50.6%	100	33.2%	$p < 0.0001$
Netherlands	152	21.3%	104	34.6%	n. s.
United Kingdom	52	7.3%	40	13.3%	$p = 0.0038$
USA	48	6.7%	0	0.0%	$p < 0.0001$
Female gender					
All patients	382/715	53.4%	180/301	59.8%	n. s.
Patients aged ≥ 18 years	148/227	65.2%	135/208	64.9%	n. s.
Caucasian race/ethnicity	570/574	99.3%	258/260	99.2%	n. s.
Age groups					
< 5 years	313	43.8%	56	18.6%	
6–17 years	174	24.3%	37	12.3%	
18–34 years	87	12.2%	81	26.9%	$p < 0.0001$
35–64 years	129	18.0%	111	36.9%	
≥ 65 years	11	1.5%	16	5.3%	
Body mass index (mean ± SD)					
Age < 18 years	16.2 ± 2.7		16.5 ± 3.1		n. s.
Age ≥ 18 years	24.1 ± 4.4		24.6 ± 4.1		n. s.
Adult smokers	38/171	22.2%	40/176	22.7%	n. s.
Cigarettes per day in smokers: median (interquartile range)	10.0	(4.0–16.5)	10.0	(7.0–15.0)	n. s.
Persons in household (mean ± SD)	3.6 ± 1.7		3.4 ± 1.3		n. s.
Total annual household income	N = 349		N = 150		
< 15,000 €	75	21.5%	31	20.7%	
15,000–29,999 €	95	27.2%	42	28.0%	
30,000–44,999 €	88	25.2%	45	30.0%	n. s.
45,000–59,999 €	47	13.5%	22	14.7%	
60,000–74,999 €	28	8.0%	7	4.7%	
≥ 75,000 €	16	4.6%	3	2.0%	
Previous treatment by physician	507/566	89.6%	236/260	90.8%	n. s.

n. s. statistically not significant.

cial diagnoses, e. g. mental handicap or scarlet fever (5.6%), other / not specified (12.1%). NE-A-patients (n = 461) did not differ from evaluable A-patients (n = 715) regarding gender or chief complaint severity; NE-A-patients were median 1.13 years younger (95%-CI: 0.38–1.95, $p = 0.0036$) and more NE-A-patients were prescribed antibiotics on Day 0 (2.8% vs. 0.8%, $p = 0.0153$).

Baseline characteristics

Demographics: A- and C-groups did not differ significantly regarding gender, race, body mass index, smoking, household size or income, or previous treatment by study physician. The groups differed significantly regarding country and age (Table 1).

Disease status at baseline: A- and C-groups had similar percentages of chief complaints / diagnoses, except sinus pain / sinusitis being less frequent in A-group. Physicians' confidence in their diagnosis was similar, but A-physicians were more likely to base diagnosis on clinical examination than C-physicians. The two groups did not differ significantly regarding baseline symptom score, SF-12 or KINDL, respiratory or other concomitant disease, ongoing medication, or patients' confidence in therapy. A-patients had more frequently fever ≥ 38.5°C, severe pain, and a recurrent chief complaint had higher severity of chief complaint, shorter complaint duration, and longer consultation time (Table 2).

96.8% (691/714) of A-patients and 65.0% (195/300) of C-patients were not willing to be randomised if their treatment would be part of a clinical trial ($p < 0.0001$). Most frequent reason for refusing randomisation was treatment preference. Altogether 94.5% of A-patients had a preference for AM, whereas 66.7% of C-patients had a preference for conventional treatment for their chief complaint.

Therapy

On Day 0, all but nine patients were prescribed medicines (Table 3). Medication was prescribed to be taken for mean 6.3 days ± 3.0 in the A-group and 4.6 days ± 2.5 in the C-group ($p < 0.0001$, median difference: 1.0 day; 95%-CI: 1.0–2.0). Physicians' confidence (0–10) in their prescription was mean 8.8 ± 1.1 and 8.0 ± 1.7 ($p < 0.0001$, median difference: 1.0, 95%-CI: 0.0–1.0). Throughout follow-up, 89.7% and 87.0% of patients reported being compliant with medication prescriptions.

Table 2. Disease status at baseline, consultation length

	Anthroposophy group (N = 715)		Conventional group (N = 301)		
	N	%	N	%	
Chief complaint					
Cough	285	39.9%	102	33.9%	n. s.
Sore throat	188	26.3%	70	23.3%	n. s.
Ear pain	143	20.0%	57	18.9%	n. s.
Sinus pain	50	7.0%	56	18.6%	p < 0.0001
Runny nose	49	6.9%	16	5.3%	n. s.
Duration of chief complaint					
0 – ≤ 24 h	192	26.9%	33	11.0%	
> 24 h – ≤ 48 h	167	23.4%	93	30.9%	
> 2 days – ≤ 3 days	134	18.7%	85	28.2%	p = 0.0043
> 3 days – ≤ 5 days	153	21.4%	62	20.6%	
> 5 days – ≤ 7 days	68	9.5%	28	9.3%	
Severity of chief complaint					
Mild	35	4.9%	16	5.3%	
Moderate	248	34.7%	122	40.5%	p = 0.0031
Severe	325	45.5%	143	47.5%	
Very severe	105	14.7%	18	6.0%	
Symptom score (0–4, mean ± SD)	1.3 ± 0.7		1.2 ± 0.6		n. s.
Severe or very severe pain*†	403/666	60.5%	152/285	53.3%	p = 0.0444
Fever ≥ 38.5 °C †	143/666	21.5%	40/285	14.0%	p = 0.0071
Diagnosis of chief complaint					
Pharyngitis / tonsillitis	185	25.9%	60	19.9%	p = 0.0449
Bronchitis	138	19.3%	42	14.0%	p = 0.0475
Otitis media	123	17.2%	39	13.0%	n. s.
Laryngitis / tracheitis	108	15.1%	43	14.3%	n. s.
Rhinitis / common cold / upper RTI unspecified	103	14.4%	48	15.9%	n. s.
Sinusitis	53	7.4%	59	19.6%	p < 0.0001
Other	5	0.7%	10	3.3%	
Physician's confidence in diagnosis (0–10, mean ± SD)	9.1 ± 1.1		9.0 ± 1.2		n. s.
– based on clinical examination	661	92.4%	247	82.1%	p < 0.0001
– based on symptoms alone	53	7.4%	53	17.6%	
Chief complaint episode within last 12 months	376	52.6%	111	36.9%	p < 0.0001
Concomitant disease present	226	31.6%	97	32.2%	n. s.
Disease of respiratory system	65	9.1%	30	10.0%	n. s.
Medication use for concomitant disease	128	17.9%	62	20.6%	n. s.
Anti-asthmatics	12	1.7%	10	3.3%	n. s.
Nasal preparations	4	0.6%	5	1.7%	n. s.
Corticosteroids for systemic use	0	0.0%	1	0.3%	n. s.
Antibacterials for systemic use	0	0.0%	0	0.0%	n. s.
SF-12 Summary Score (mean ± SD)	32.2 ± 5.8		33.5 ± 6.5		n. s.
KINDL Summary Score (mean ± SD)	44.9 ± 6.9		43.4 ± 5.6		n. s.
Does patient have confidence that the treatment will solve his/her medical problem? (yes/no) -yes	556/560	99.3%	258/262	98.5%	n. s.
Consultation length					
< 5 min	8	1.1%	62	20.6%	
> 5 – ≤ 15 min	442	61.8%	217	72.1%	p < 0.0001
> 15 – ≤ 30 min	261	36.5%	22	7.3%	
> 30 – ≤ 60 min	4	0.6%	0	0.0%	

* Throat, ear or sinus pain, pain on coughing; †not documented in patients with chief complaint runny nose; *n. s.* statistically not significant.

Table 3. Therapy prescribed on Day 0

Therapy	Anthroposophy Group (N = 715)		Conventional Group (N = 301)		
	N	%	N	%	
Anthroposophic medicines	715	100.0%	0	0.0%	p < 0.0001
Homeopathic medicines	96	13.4%	0	0.0%	p < 0.0001
Herbal medicines	80	11.2%	10	3.3%	p < 0.0001
Other medicines (not anthroposophic, homeopathic, or herbal)	72	10.1%	292	97.0%	p < 0.0001
No medicines	0	0.0%	9	3.0%	p < 0.0001
External applications	61	8.5%	Not documented		

N patients with prescribed therapy. Multiple responses possible.

A-patients were prescribed mean 3.0 ±1 .5 (range 2–9) AM medicines on Day 0 and 0.3 ±0.87 (range 0-8) further AM medicines during follow-up. Altogether 265 different AM medicines were prescribed; four AM medicines were prescribed to at least 10% of A-patients: Plantago Bronchial Balm (prescribed to 122/715 A-patients = 17.1%), Erysidoron® 1 Liquid (14.0%), Cinnabar comp. Powder (13.6%), Cinnabar / Pyrite Tablets (10.1%).

On Day 0, antibacterial agents were prescribed to 26.6% of C-patients and 0.8% of A-patients (p < 0.0001). During follow-up this difference increased (Table 4). Anti-inflammatory agents, analgesics, and antihistamines were also prescribed significantly more often in the C-group. Antibiotic prescription was less frequent among A-patients in all countries, age groups, and diagnosis groups.

Patient outcomes

The primary outcome, response rate after 14 days, was 89.7% in A-patients and 84.4% in C-patients (Table 5). The one-sided test confirmed non-inferior outcome in the A-group (p < 0.00001) and the odds ratio (OR) for response (A- vs. C-group) was 1.60 (95%-CI: 1.08–2.38); thus a test for superiority was performed. This test demonstrated a significant difference in favour of the A-group (p = 0.0198).

Response was significantly more frequent in A-patients than in C-patients on Day 7 (OR: 1.72, 95%-CI: 1.28–2.31, p = 0.0004) but not on Day 28 (OR: 1.08, 95%-CI: 0.58–2.03, p = 0.8714). Complete recovery was more frequent in A-patients on Day 7 (OR: 1.45, 95%-CI: 1.06–1.98, p = 0.0221), Day 14 (OR: 1.83, 95%-CI: 1.39–2.40, p < 0.0005), and Day 28 (OR: 1.59, 95%-CI: 1.14–2.21, p = 0.0064).

Improvement within 24 hours occurred in 30.9% (221/715) of A-patients and 16.6% (50/301) of C-patients (OR: 2.25, 95%-CI: 1.59–3.16, p < 0.0001), improvement within 3 days in 73.1% and 57.1% (OR: 2.04, 95%-CI: 1.54–2.71, p < 0.0001) (Fig. 2).

Improvement, response and recovery rates differed considerably between chief complaint subgroups. Comparing adults with children, outcome rates were consistently higher in A-children than in C-children, but similar in A-adults and C-adults (Table 6).

63.2% (452/715) of A-patients and 48.5% (146/301) of C-patients were very satisfied with their treatment (OR: 1.79, 95%-CI: 1.36–2.36, p < 0.0001), 31.2% and 44.5%

Table 4. Prescription on Day 0 and cumulative prescription on Days 0–28: Six most common Anatomical Therapeutic Chemical (ATC) drug groups. Percentage of patients receiving a prescription

Anatomical Therapeutic Chemical (ATC) group	Day 0					Cumulative: Day 0–28				
	A-Group		C-Group			A-Group		C-Group		
	N	%	N	%		N	%	N	%	
J01 Antibacterials for systemic use	6	0.8%	80	26.6%	p < 0.0005	39	5.5%	101	33.6%	p < 0.0001
M01 Anti-inflammatory and antirheumatic products	2	0.3%	24	8.0%	p < 0.0001	2	0.3%	26	8.6%	p < 0.0001
N02 Analgesics	14	2.0%	65	21.6%	p < 0.0001	23	3.2%	66	21.9%	p < 0.0001
R01 Nasal preparations	127	17.8%	61	20.3%	n. s.	137	19.2%	67	22.3%	n. s.
R05 Cough and cold preparations	130	18.2%	46	15.3%	n. s.	147	20.6%	56	18.7%	n. s.
R06 Antihistamines for systemic use	0	0.0%	14	4.7%	p < 0.0001	1	0.1%	16	5.3%	p < 0.0001

A-Group n = 715; *C-group* n = 301; *n. s.* statistically not significant.

Table 5. Treatment outcome on Days 7, 14 and 28. Last observation carried forward

Treatment outcome	Day 7				Day 14				Day 28			
	A-Group		C-Group		A-Group		C-Group		A-Group		C-Group	
	N	%	N	%	N	%	N	%	N	%	N	%
Complete recovery	218	30.5%	70	23.3%	459	64.2%	149	49.5%	597	83.5%	229	76.1%
Major improvement	333	46.6%	129	42.9%	182	25.5%	105	34.9%	85	11.9%	57	18.9%
Slight to moderate improvement	74	10.3%	51	16.9%	44	6.2%	29	9.6%	22	3.1%	10	3.3%
No change	15	2.1%	12	4.0%	9	1.3%	7	2.3%	8	1.1%	4	1.3%
Deterioration	5	0.7%	3	1.0%	7	1.0%	7	2.3%	3	0.4%	1	0.3%
Missing	70	9.8%	36	12.0%	14	2.0%	4	1.3%	0	0.0%	0	0.0%
Total	715	100.0%	301	100.0%	715	100.0%	301	100.0%	715	100.0%	301	100.0%
Response (complete recovery or major improvement)	551	77.1%	199	66.1%	641	89.7%	254	84.4%	682	95.4%	286	95.0%

satisfied, 3.5% and 4.0% neutral, 1.7% and 2.3% dissatisfied, 0.0% and 0.7% very dissatisfied, 0.4% and 0.0% missing. 69.9% and 60.5% of patients were very satisfied with their physician (OR: 1.52, 95%-CI: 1.15–2.01, $p = 0.0043$). 95.7% of A-patients and 83.4% of C-patients would choose the same therapy again for their chief complaint ("yes" at all follow-ups) (OR: 4.40, 95%-CI: 2.74–7.04, $p < 0.0001$); 98.9% and 96.3% would choose the same physician again (OR: 3.35, 95%-CI: 1.34–8.42, $p = 0.0101$).

Unadjusted odds ratios (A- vs. C-) were analysed for the eight major outcomes in the 25 subgroups pertaining to the seven prognostic variables (details in Methods section, altogether 200 comparisons). Odds ratios favoured A-patients for 184 comparisons and C-patients for 16 comparisons.

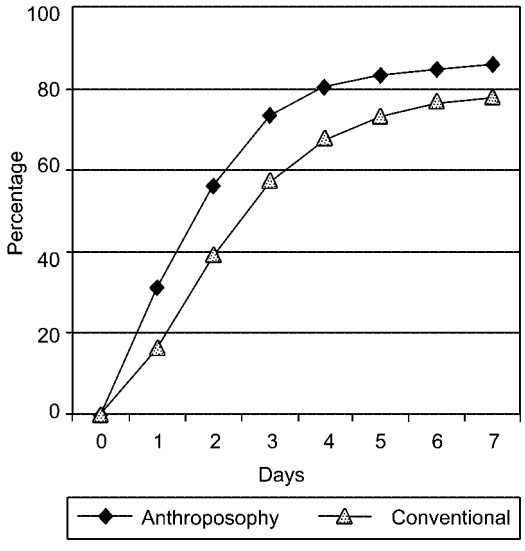

Fig. 2. First improvement, cumulative percentage. A-group: n = 715; C-group n = 301

Major outcomes were adjusted for the seven prognostic variables. Adjustment for age had the strongest effects on results, reducing the odds ratios by a value ranging from 0.25 (satisfaction with treatment: unadjusted OR 1.79, adjusted OR 1.54) to 0.62 (improvement within 24 h: unadjusted OR 2.25, adjusted OR 1.63). Adjusting for the other six variables individually had little effects. After multiple logistic regression, adjusting for all seven variables, all odds ratios favoured the A-group; results were statistically significant for improvement within 1 or 3 days, response by Day 7, and patients' choice of same therapy again (Table 7).

Adverse drug reactions were reported in 2.7% (19/715) of A-patients and 6.0% (18/301) of C-patients (OR for no adverse reaction: 2.33, 95%-CI: 1.21–4.50, $p = 0.0157$). One (0.1%) A-patient and three (1.0%) C-patients reported adverse reactions of severe intensity (complete impairment of normal daily activities). Serious Adverse Events (SAE) occurred in 4/715 A-patients and 3/301 C-patients. All SAE were acute hospitalisations. SAE in A-patients: 1) patella fracture, 2) asthma, mesenteric adenitis, 3) gastroenteritis, vomiting, hypovolaemia, 4) suspected meningitis (suspicion not confirmed). SAE in C-patients: 5) knee arthroscopy, 6) emotional lability, 7) tonsillectomy. At the last follow-up, SAE 1 + 6 were still being treated, other SAE had subsided. None of these SAE was related to any medication. Among patients excluded from the analysis (n = 155) one SAE was reported in a C-patient: acute hospitalisation with pneumonia, caused by medication, outcome: permanent health damage.

Discussion

Overall study findings

This study compared primary care patients self-selected to treatment by anthroposophic (n = 715 A-patients) or conventional physicians (n = 301 C-patients) for acute sore throat, ear pain, sinus pain, runny nose or cough. The primary hypothesis was confirmed that the response rate on day 14 would not be lower in A-patients than in

Table 6. Cumulative percentage of A- and C-patients with *FI* = first improvement, *MI* = major improvement, *CR* = complete recovery. Subgroup analysis according to chief complaint and age

Subgroups	Number of patients		Percentages of patients											
			1 day FI		3 days FI		7 days MI + CR		7 days CR		14 days MI + CR		14 days CR	
	A-	C-	A-	C-	A-	C-	A-	C-	A-	C-	A-	C-	A-	C-
Cough	285	102	23.5	8.8	71.2	52.0	71.6	65.7	17.2	10.8	88.4	81.4	58.6	40.2
Sore throat	188	70	29.8	14.3	73.9	55.7	81.4	72.9	40.4	38.6	89.9	90.0	73.4	62.9
Ear pain	143	57	53.8	26.3	82.5	68.4	89.5	63.2	46.9	33.3	95.1	84.2	74.8	61.4
Sinus pain	50	56	24.0	19.6	64.0	55.4	76.0	62.5	16.0	17.9	90.0	83.9	38.0	39.3
Runny nose	49	16	18.4	31.3	63.3	62.5	57.1	62.5	36.7	18.8	79.6	81.3	57.1	50.0
Age 0–17 y	487	93	37.0	16.1	79.1	59.1	82.3	61.3	35.1	29.0	93.0	86.0	71.0	55.9
Age ≥ 18 y	227	208	17.6	16.3	60.4	56.3	65.6	68.3	20.7	20.7	82.4	83.7	49.8	46.6
All patients	715	301	30.9	16.6	73.1	57.1	77.1	66.1	30.5	23.3	89.7	84.4	64.2	49.5

C-patients. On the contrary, this and other major outcome rates (improvement within 1 or 3 days, response and recovery by Days 7 and 14) were significantly higher in the A-group. After adjustment for age, gender, country, and four baseline symptom variables, all odds ratios still favoured the A-group; results were statistically significant for early outcomes (improvement by 1 or 3 days, response by Day 7).

During the four-week study period, A-patients were less frequently prescribed antibiotics, analgesics, and anti-inflammatory drugs, and reported adverse drug reactions less frequently than C-patients. Complications related to chief complaint or its treatment occurred in two C-patients and no A-patient. Patient satisfaction was higher in the A-group.

Internal validity

The primary outcome, Day 14 response rate, was adopted from a similar study on homeopathy [55]. However, this is an *insensitive measure* [56] of outcome differences, since most acute respiratory infections will have improved after 14 days. A follow-up period of 14 days is longer than in randomised trials of acute sinusitis, bronchitis (average 10 days), pharyngitis, otitis and common cold (1–7 days) [3, 13–16, 57]. Thus the four secondary outcomes analysed after 1, 3, and 7 days would seem more appropriate.

Since several clinical outcomes were analysed, the issue of *multiple hypothesis-testing* arises. However, all comparisons favoured the A-group. Moreover, the time sequence of outcome rates and odds ratios (Table 7) is compatible with short-term effects (improvement by 1 and 3 days, response by Day 7) becoming attenuated by subsequent improvement in most patients (response by Day 14). This consistency and plausibility of results suggests that although the estimated *sample size* was not reached, the study was not underpowered to allow for a valid interpretation.

Attrition bias: Patients with at least one evaluable follow-up interview on Day 7, 14 or 28 (n = 1016 of 1171 enrolled patients) were included in the analysis; patients without any evaluable follow-ups (n = 155) were excluded. Analysis of excluded patients suggests that any attrition bias, if present, would be conservative, i. e. disfavouring the A-group, since evaluable A-patients had significantly higher baseline symptom severity than excluded A-patients (mean 1.3 vs. 1.0), whereas no such difference was observed in the C-group. Most exclusions were unrelated to treatment or clinical outcome. In 99 patients the interviews were not performed according to protocol. 56 patients had no follow-up interview; only seven of these patients refused to be interviewed.

For outcome analysis of included patients, missing data from Days 14 or 28 were replaced by last observation carried forward when available; residual missings were classified as non-responder. Proportions of included patients with residual missing data did not differ significantly between A- and C-groups. We tested the impact of different missing data analyses on improvement, response and recovery rates: Patients without any follow-ups or with residual missings were alternatively classified as non-responder, or as responder, or were excluded from analysis; Day 14 outcomes were analysed with and without last observation carried forward of Day 7 data. Altogether 31 alternative analyses were performed. All analyses resulted in higher outcome rates in the A-group than in the C-group; in 28/31 analyses, these differences were statistically significant. In conclusion, neither attrition bias as such, nor alternative ways of analysing missing data would change overall study results.

Observation and reporting bias: This study focused on patient-relevant outcomes [13, 36, 58] i. e. the patients' own account of improvement, recovery, therapy satisfaction, and adverse effects. Patient blinding was neither desirable nor possible, since blinding would have impeded real-world treatment, e. g. dose titration of AM medication. Patient self-observation can be biased e. g. through expectations from the therapy or gratefulness towards the physician [56], but these factors were similarly strong in both groups. To diminish potential obsequious-

Table 7. Major outcomes: outcome rates, unadjusted odds ratios (OR) with 95% confidence intervals, and odds ratios after multiple logistic regression, adjusting for country, gender, age, chief complaint, duration of complaint, complaint episode within last 12 months, and baseline symptom score. Odds ratio > 1 indicates better outcome in A-group

Outcome	Outcome rate				Unadjusted odds ratio (A- vs. C-)		Adjusted odds ratio (A- vs. C-)	
	A-Group (N = 715)		C-Group (N = 301)					
	N	%	N	%	OR	(95%-CI)	OR	(95%-CI)
First improvement ≤ 24 hours	221	30.9%	50	16.6%	2,25	(1,59–3,16)	1,54	(1,03–2,31)
First improvement ≤ 3 days	523	73.1%	172	57.1%	2,04	(1,54–2,71)	1,61	(1,16–2,22)
Response on Day 7	551	77.1%	199	66.1%	1,72	(1,28–2,31)	1,50	(1,07–2,11)
Response on Day 14	641	89.7%	254	84.4%	1,60	(1,08–2,38)	1,29	(0,82–2,00)
Recovery on day 7	218	30.5%	70	23.3%	1,45	(1,06–1,98)	1,05	(0,72–1,54)
Recovery on day 14	459	64.2%	149	49.5%	1,83	(1,39–2,40)	1,35	(0,98–1,86)
Very satisfied with treatment*	452	63.2%	146	48.5%	1,79	(1,36–2,36)	1,39	(0,98–1,95)
Choosing this therapy again*	684	95.7%	251	83.4%	4,40	(2,74–7,04)	3,54	(2,13–5,90)

* At all available follow-ups.

ness bias, follow-up data were not collected at physicians' offices but by telephone. For technical reasons, blinding of telephone interviewers towards the anthroposophic setting was not possible. However, reporting bias is unlikely, since all interviews followed identical protocols and were performed by independent interviewers without financial or personal ties to any treatment regimen or any physician. Since adverse drug reactions were reported by patients only and not medically confirmed, true rates may be lower, possibly blunting the observed group difference.

Baseline differences: This non-randomised study compared patients who had chosen to be treated by anthroposophic or conventional physicians. It was not a purpose of this real-world comparison to have identical baseline groups. The largest differences observed pertained to country, age, frequency of chief complaint sinus pain, and recurrences of chief complaint. To control for confounding, outcomes were adjusted for these variables, and for gender, duration of chief complaint, and symptom severity. Other variables known to affect the clinical course of RTI/AOM were either not present (e. g. ongoing antibiotic use, cystic fibrosis, AIDS, conditions in study exclusion criteria list), present in only 0.1% (heart failure) to 2.2% (chronic respiratory disease requiring medication) of patients, or were similar in both groups (smoking). Nevertheless, residual confounding cannot be excluded. More important: factors related to patients' self-selection (e. g. lifestyle or motivation, independent of or due to the AM approach) may have affected outcomes. For example, anthroposophic treatment of infections often entails more active engagement (frequent dosing of medication, extended nursing) than conventional therapy, which may not be acceptable to all patients [59]. Thus, although adjusted outcomes were more favourable in the AM group, one cannot conclude that AM treatment would have been "better" for the patients receiving conventional care; one can only say that patients choosing AM therapy had better outcomes than patients receiving conventional treatment.

Representativity of participants

Settings and physicians: Patients were recruited by 36 physicians from 23 municipalities in five countries, allowing for a range of healthcare settings.

Eligibility criteria: In primary care, patients seek relief of symptoms, not diagnoses. General practitioners' treatment of RTI/AOM relies more on symptoms and signs than diagnoses or tests [12, 39, 60–62]. Whereas clinical trials traditionally include patients with specific diagnoses, academic primary care medicine is now calling for trials focusing on patients' symptoms, to mirror the full disease spectrum seen in real-world practice [58]. In this study, we included patients with one out of five symptoms; patients were not required to fulfil a set of diagnostic criteria, the clinical and prognostic validity of which is often disputable. (E. g. diagnosis "streptococcal pharyngitis": Bacterial pharyngitis is not more severe or long-lasting than viral [36], and in a Cochrane review, antibiotics were only moderately more effective in patients with positive Streptococci throat cultures compared to patients without Streptococci [3]).

Eligible vs. enrolled patients: Screening data suggest that enrolled A-patients are representative for eligible A-patients: Reasons for non-inclusion of eligible A-patients (NE-A) were time constraints or technical obstacles in 80%. NE-A-patients (n = 461) were similar to evaluable A-patients (n = 715) regarding age, gender, chief complaint severity, and antibiotic prescription. For the C-group no screening data were available, thus representativity of enrolled C-patients cannot be assessed.

Generalisability of study results

Patient numbers were limited in two subgroups: Only 16 C-patients had chief complaint runny nose, and only 27

A + C-patients were over 65 years. Children aged 0–17 years had consistently more favourable clinical outcomes in A-group than in C-group, whereas adults had similar results in both groups (Table 6). Antibiotic prescription rates were lower in A-patients across all ages. Thus, study results apply to patients aged < 65 with ear, throat, or sinus pain or cough, and the superior clinical outcomes of AM compared to conventional treatment may not be generalisable to adults.

Study implications

Implication for practice: Study results suggest that anthroposophic treatment of primary care patients with acute respiratory and ear infections is safe and at least as effective as conventional treatment. In addition, anthroposophic treatment allows for a very low use of antibiotics, analgesics and anti-inflammatory drugs.

The low antibiotic use (0.8% of A-patients vs. 26.6% of C-patients at study entry, 5.5% vs. 33.6% throughout the study) cannot be explained by mild symptoms: at study entry, 14.7% of A-patients and 6.0% of C-patients had very severe symptoms, 52.7% vs. 37.0% had recurrent symptoms. Similarly, very few A-patients were prescribed analgesics (2.0% vs. 21.6% at baseline) or anti-inflammatory drugs (0.3% vs. 8.0%), although at baseline severe pain (60.5% vs. 53.3%) and fever (21.5% vs. 14.0%) were more frequent in the A-group. Thus, in anthroposophic treatment settings, the use of drugs with unfavourable ecological (antibiotic resistance) or physiological properties (antipyretics suppress physiological responses to infection [63, 64]) or with potential for severe adverse effects [65–68] can be drastically reduced, compared to conventional practice.

One could argue that this non-prescription of antibiotics and other drugs would be the only true benefit demonstrated from anthroposophic treatment, since "RTI and AOM are self-limiting conditions, antibiotics only make things worse, thus the inferior outcome after conventional therapy could be due to detrimental effects of unnecessary antibiotics". For several reasons, this argumentation does not hold: Firstly, not all RTI/AOM patients are cured spontaneously; some develop otitis media with effusion [5], subacute/chronic sinusitis [62] etc. In this study, for example, 16.5% of A-patients and 23.9% of C-patients had not recovered after 28 days. Secondly, it has not been demonstrated that antibiotics are worthless for all RTI/AOM patients, because studies testing whether antibiotics work (placebo-controlled antibiotic trials) frequently exclude patients deemed to require antibiotics (patients "too ill", with recurrences, with several organs affected). Thirdly, if antibiotics had detrimental effects on the short-term outcomes studied here, patients receiving antibiotics would fare worse than patients without antibiotics. Cochrane-reviews of placebo-controlled antibiotic trials, however, [3, 13–16], did not find worse, but equal or slightly better short-time outcomes in the antibiotic groups compared to the placebo groups.

Finally, there is no evidence that the conventional physicians of this study were over-prescribing antibiotics by current standards. On the contrary, antibiotic prescription was less frequent in the C-group (27% of patients at study entry) than in recent primary care samples (pharyngitis: 49–94%, AOM: 81–97%, sinusitis: 80–91%, bronchitis: 69–89%, cough: 70%, any RTI: 39–54% [4, 7–12, 69–73]). In conclusion: in anthroposophic settings, antibiotics could be avoided in almost all RTI/AOM patients, including those usually deemed to require antibiotics. Moreover, anthroposophic treatment had more favourable short-term outcomes than "modern" conventional therapy with moderate antibiotic use.

Implication for research: In this study, 265 different AM medicines were prescribed for RTI/AOM; only four medicines were prescribed for > 10% of patients. Thus, single-drug trials, albeit often requested for regulatory purposes, will cover only small segments of real-world AM practice, and will not be feasible in many cases. Therefore, study designs enabling simultaneous evaluation of many AM medicines should be developed and implemented.

At study entry, physicians asked patients if they would be willing to be randomised if their treatment was offered in a clinical trial. 97% of AM patients would not be willing to be randomised. Thus, for studying AM therapy of acute infections (and probably other conditions) in the usual setting, randomisation does not seem feasible. (Even if patients' answers might have been influenced by their physicians, randomisation – which of course depends on both physicians' and patients' willingness – would still seem infeasible in AM settings.) If, on the other hand, randomised trials of AM should be conducted in other settings, results may lack representativity and be misleading.

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