Outcome of anthroposophic medication therapy in chronic disease: A 12-month prospective cohort study

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Background: Anthroposophic medications (AMED) are prescribed in 56 countries.
Objective: To study clinical outcomes in patients prescribed AMED for chronic disease.
Design: Prospective cohort study.
Setting: 110 medical practices in Germany.
Participants: 665 consecutive outpatients aged 1–71 years, prescribed AMED for mental, respiratory, musculoskeletal, neurological, genitourinary, and other chronic diseases.
Main outcomes: Disease and Symptom Scores (physicians' and patients' assessment, 0–10) and SF-36.
Results: During the first six months, an average of 1.5 AMED per patient was used, in total 652 different AMED. Origin of AMED was mineral (8.0% of 652 AMED), botanical (39.0%), zoological (7.2%), chemically defined (13.0%), and mixed (33.0%). From baseline to six-month-follow-up, all outcomes improved significantly: Disease Score improved by mean 3.15 points (95% confidence interval 2.97–3.34, $p < 0.001$), Symptom Score by 2.43 points (2.23–2.63, $p < 0.001$), SF-36 Physical Component Summary by 3.04 points (2.16–3.91, $p < 0.001$), and SF-36 Mental Component Summary by 5.75 points (4.59–6.92, $p < 0.001$). All improvements were maintained at 12-month follow-up. Improvements were similar in adult men and women, in children, and in patients not using adjunctive therapies.
Conclusion: Outpatients using AMED for chronic disease had long-term reduction of disease severity and improvement of quality of life.
Keywords: anthroposophy, chronic disease, drug therapy, outcome and process assessment (health care), prospective studies, quality of life

Background

In the developed world, the most frequent reason for people to seek health care is a chronic disease (Dowrick et al 2005). Chronic diseases are the most common cause of disease burden worldwide, are often associated with comorbidity, and are rarely completely cured (Dowrick et al 2005). Many patients with chronic disease use complementary therapies (Eisenberg et al 1998; Al Windi 2004), sometimes provided by their physicians.

One such physician-provided complementary therapy system is anthroposophic medicine (AM), founded by Rudolf Steiner and Ita Wegman (Steiner and Wegman 2000). AM acknowledges a spiritual – existential dimension in man, which is assumed to interact with psychological and somatic levels in health and disease. AM therapy for chronic disease aims to counteract constitutional vulnerability, stimulate salutogenetic self-healing capacities, and strengthen patient autonomy (Evans and Rodger 1992; Ritchie et al 2001; Kienle et al 2006a). This is sought to be achieved by counseling (Ritchie et al 2001), by nonverbal artistic therapies such as painting or clay

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(Collot d'Herbois 1993; Hauschka-Stavenhagen 1997), music (Maurer 1994) or speech exercises (Lorenz-Poschmann 1982), by eurythmy movement exercises (Kirchner-Bockholt 1977), by physical therapies (Hauschka-Stavenhagen 1990; Ostermann et al 2003), and by special anthroposophic medications (AMED). A key concept of AMED therapy is typological correspondences between pathophysiological processes in man and formative forces working in minerals, plants, and animals, reflecting a common evolution of man and nature (Evans and Rodger 1992; Steiner and Wegman 2000; Ritchie et al 2001; Kienle et al 2006a). These correspondences go beyond the *simile* principle of homeopathy (a remedy taken in concentrated form induce symptoms which are treated by the same remedy taken in homeopathic potencies*) and are used therapeutically in medications of mineral, botanical or zoological origin, and in chemically defined substances. The manufacturing of AMED products includes special pharmaceutical processes which are rarely used for homeopathic remedies and other non-AMED products: eg, the production of metal mirrors by chemical vapor decomposition, and the processing of herbs by fermentation, toasting, carbonizing, incineration or digestion (heat treatment at 37 °C). AMED can be prepared in concentrated form or in homeopathic potencies, but unlike homeopathy, AMED products are rarely prepared in potencies higher than D30*. Moreover, AMED products are administered in various ways (oral, rectal, vaginal, conjunctival, nasal or percutaneous application, or by subcutaneous, intracutaneous or intravenous injection). Typically, AMED products in concentrated form and oral or rectal administration are used to affect pathophysiological processes seen to originate in the metabolic system; AMED products in decimal potencies up till D12–D15 and AMED administration by injections are used to affect rhythmical processes such as respiration and circulation; while AMED products in decimal potencies of D20–D30 and external applications are used to treat pathology originating in the sense-nervous system (Husemann and Wolff 1987; Anonymous 2005c). AMED therapy can be standardized (eg, Ferrum-Quarz Capsules for migraine, Meteoric Iron Globuli for fatigue) or individualized (involving one or several AMED products and sometimes nonmedication AM therapies) (Kienle et al 2006a). A number of standardized AMED therapy regimens can be prescribed by any physician, while individualized AMED treatment requires special training. Accordingly, in Europe, AMED products are prescribed by approximately 30,000 physicians (Anonymous 2005b), while 2000 certified AM physicians also provide individualized therapy (Anonymous 2005a). Worldwide, AM physicians work in 56 countries (Anonymous 2004). Prior to prescription of individualized AMED treatment or referral to other AM therapies, AM physicians have prolonged consultations with their patients. These consultations are used to take an extended history, to address constitutional, psychosocial, and biographic-existential aspect of patients' illness, to explore the patient's preparedness to engage in treatment, and to select optimal therapy for each patient (Evans and Rodger 1992; Ritchie et al 2001).

Because of the large number of AMED in use (currently more than 2,000 different AMED products are on the market [Anonymous 2005b]), clinical studies of single AMED for single indications are feasible for only a small proportion of AMED. Most such studies conducted up till now concerned mistletoe products for cancer (Kienle et al 2006a; Kienle and Kiene 2007). Moreover, since AMED therapy for chronic disease is often individualized (Kienle et al 2006a), a whole-system evaluation approach may be more appropriate than single medication studies (Fonnebo et al 2007). Here we present a study of AMED therapy for chronic diseases, evaluated as a whole system.

Methods

Objective and design

This is a prospective cohort study in a real-world medical setting. The study was part of a research project on the effectiveness and costs of AM therapies in outpatients with chronic disease (Anthroposophic Medicine Outcomes Study, AMOS) (Hamre et al 2004, 2006b). The AMOS project was initiated by a health insurance company in conjunction with a health benefit program. The primary research question of the present study was: Is physician-prescribed AMED therapy for chronic disease associated with clinically relevant improvement of disease symptoms? Further research questions addressed quality of life, use of adjunctive therapies, adverse reactions, and therapy satisfaction.

Setting, participants, and therapy

All physicians certified by the Physicians' Association for Anthroposophical Medicine in Germany and working in an office-based practice or outpatient clinic were invited to participate in the study. Certification as an AM physician required a completed medical degree and a three-year structured postgraduate training. The participating physicians

*All homeopathic and many anthroposophic medications are 'potentized', ie, successively diluted, each dilution step involving a rhythmic succussion (repeated shaking of liquids) or trituration (grinding of solids into lactose monohydrate). A D30 potency (also called 30X) has been potentized in a 1:10 dilution for 30 times, resulting in a $1{:}10^{-30}$ dilution.

recruited consecutive patients starting AM therapy. Patients enrolled in the period 1 January 1999 to 31 December 2005 were included in the present analysis if they fulfilled the eligibility criteria.

The following inclusion criteria were used: (i) Outpatients aged 1–75 years; (ii) AM-related consultation of at least 30 minutes or referral to AM therapy (art, eurythmy or rhythmical massage) for any indication (main diagnosis); (iii) duration of main diagnosis of at least 30 days at study enrolment; (iv) new prescription of at least one AMED for main diagnosis at study enrolment.

Patients were excluded if they had previously received AM (see [ii] of inclusion criteria) for their main diagnosis. Medications were classified as AMED products (any medication produced by Abnoba Arzneimittel GmbH, Pforzheim, Germany; Helixor Heilmittel GmbH and Co, Rosenfeld, Germany; WALA Heilmittel GmbH, Eckwälden, Germany; or Weleda AG, Schwäbisch-Gmünd, Germany) and non-AMED products (all other medications). Patients were treated at the physicians' discretion; physicians were thus free to individualize treatment. AMED therapy was evaluated as a whole system, including physician-patient interactions. Additional costs for AM treatments were 0.1–5.2 Euro per daily dose of an AMED (51 different price groups, median 0.2 Euro, mean 0.8 Euro); 20–32 Euro per AM therapy session; and 46 Euro and 92 Euro for AM consultations with physician of 30 min and 60 min duration, respectively. These costs were reimbursed by some but not all German health insurance companies.

Clinical outcomes

Disease severity

Primary outcome was disease severity at six-month follow-up. Disease severity was assessed on numerical rating scales (Downie et al 1978) from 0 ("not present") to 10 ("worst possible"): *Disease Score* (physician's global assessment of severity of main diagnosis); *Symptom Score* (patients' assessment of one to six most relevant symptoms present at baseline). Disease Score was documented after 0 and 6 months, Symptom Score and quality of life outcomes (see below) after 0, 3, 6, and 12 months.

Quality of life

In adults (17–75 years) quality of life was assessed with SF-36® *Health Survey*, a widely used self-report measure of functional impairment and disability. SF-36 comprises 36 questions yielding eleven scores: the SF-36 Physical and Mental Component Summary Measures, the eight SF-36 subscales, and the SF-36 Health Change item (Bullinger et al 1998).

In children aged 8–16, quality of life was assessed with self-report, using the *KINDL® Questionnaire for Measuring Health-Related Quality of Life in Children and Adolescents*, Total Quality of Life Score. For patients enrolled up till March 2001 the KINDL 40-item version (Ravens-Sieberer and Bullinger 1998) was used; for patients enrolled April 2001 and thereafter the KINDL 24-item version (Ravens-Sieberer and Bullinger 2000) (*Kid-KINDL®* for age 8–12, *Kiddo-KINDL®* for age 13–16) was used. The KINDL questionnaire addresses physical and emotional well-being, self-esteem, family, friends, and everyday functioning.

In children aged ≤7 years, quality of life was assessed by caregivers. For patients enrolled up till March 2001 the *KITA Quality of Life Questionnaire* (Wittorf 2001) (age 1–7) was used. The KITA questionnaire comprises the subscales Psychosoma and Daily Life. For patients enrolled April 2001 and thereafter *Kiddy-KINDL®*, Total Quality of Life Score (Ravens-Sieberer and Bullinger 2000) (age 4–7) was used.

Other outcomes

Patients rated therapy outcome (0–10) and satisfaction with therapy (0–10) after 6 and 12 months. Adverse drug reactions were documented by patients after 6 and 12 months, and by physicians after 6 months (for patients enrolled before 1 April 2001 also after 3, 9, and 12 months). Documentation included suspected cause, intensity (mild/moderate/severe = no/some/complete impairment of normal daily activities), and therapy withdrawal because of adverse reactions. Serious adverse events (death, life-threatening condition, acute in-patient hospitalization, new disease or accident causing permanent disability, congenital anomaly, new malignancy) were documented by physicians.

Data collection

All data were documented with questionnaires sent in sealed envelopes to the study office. Physicians documented eligibility criteria and medication prescription; all other items were documented by patients (by caregivers of children <17 years) unless otherwise stated. Patient responses were not made available to physicians.

Medication use in the preceding 3 (or 6) months was documented at each follow-up after 3, 6, and 12 months (name, administration frequency [daily, 3–6 days per week, 1–2 days per week, 1–3 days per month, <1 day per month] and duration of use). Physicians were compensated 40 Euro per included and fully documented patient; patients received no compensation.

Data were entered twice by two different persons into Microsoft® Access 97 (Microsoft Corporation, Richmond,

VA, USA). The two datasets were compared and discrepancies resolved by checking with the original data.

Quality assurance, adherence to regulations

The study was approved by the Ethics Committee of the Faculty of Medicine Charité, Humboldt University, Berlin, Germany, and was conducted according to the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Written informed consent was obtained from all patients before enrolment.

Data analysis

Data analysis (SPSS® 14.0.1, SPSS Inc., Chicago, Ill, USA; StatXact® 5.0.3, Cytel Software Corporation, Cambridge, MA, USA) was performed on all patients fulfilling eligibility criteria for this study. For continuous data t-test was used. For binominal data McNemar test and Fisher's exact test were used. All tests were two-tailed. Significance criteria were $p < 0.05$ and 95% confidence interval (95% CI) not including 0. Since this was a descriptive study, no adjustment for multiple comparisons was performed (Feise 2002). Pre-post effect sizes were calculated as Standardized Response Mean (= mean change score divided by the standard deviation of the change score) and classified as small (0.20–0.49), medium (0.50–0.79), and large (≥0.80) (Liang et al 1990).

For analysis of medication use, missing data on administration frequency were replaced by the value 3/7 (three times weekly) for AMED ampoules for injection, and 1 (daily) for all other medications; missing data on duration of AMED or non-AMED use were replaced by average duration of AMED and non-AMED use, respectively, during the follow-up period in question. AMED with identical ingredients and dosage form but different concentrations were grouped together. For each medication, the number of patient-months was calculated as 'duration of use' × F (where F = 1 for medication taken daily, 3–6 days per week or 1–2 days per week; F = 1/15 for medication taken 1–3 days per month; F = 0 for medication taken <1 day per month). The number of patient-months for all AMED, all non-AMED, and for relevant medication subgroups was calculated as the sum of all patient-months in question. Clinical outcomes were analyzed in patients with evaluable data for each follow-up, without replacement of missing values.

Five pre-planned sensitivity analyses (SA1-SA5) were performed to assess the influence of patient attrition, natural recovery, adjunctive nonmedication AM therapies, and adjunctive diagnosis-relevant non-AM therapies on the 0–6-month Disease Score outcome. SA1 was a preparatory analysis, necessary to perform two subsequent analyses (SA3 and SA5, see below) and was retained in all subsequent analyses: The sample was restricted to patients with six-month-patient-follow-up questionnaire available. SA2 concerned attrition bias: Missing values after six months were replaced with the baseline value carried forward. SA3 concerned the effect of adjunctive AM therapies (eurythmy, art, and rhythmical massage therapy): The sample was restricted to patients using no such therapy in the first six study months. SA4 concerned natural recovery, which was assumed to be unlikely in AMOS patients with disease duration of at least one year (Hamre et al 2007a). The sample was restricted to patients with disease duration of at least 12 months prior to study enrolment. SA5 concerned the effects of relevant non-AM adjunctive therapies, and was performed on patients with a main diagnosis of mental, respiratory or musculoskeletal diseases, headache syndromes or menstruation-related gynecological disorders. In SA5, this sample was restricted to patients not using diagnosis-related adjunctive therapies during the first six study months.

Results

Participating physicians

A total of 110 physicians enrolled patients into the study; these physicians did not differ significantly from AM-certified physicians in Germany not enrolling patients (n = 286) regarding age (mean ± SD: 47.1 ± 7.1 vs 48.8 ± 8.3 years), number of years in practice (18.4 ± 7.7 vs 19.6 ± 9.2 years) or the proportion of primary care physicians (82.7% vs 85.9%). The percentage of men was higher in AM physicians enrolling patients (50.9%) than in AM physicians not enrolling patients (33.9%) (p = 0.003).

Patient recruitment and follow-up

From 1 January 1999 to 31 December 2005, a total of 1,905 patients were assessed for eligibility. Of these patients, 665 fulfilled all eligibility criteria and were included in the analysis. Of the 1,240 patients who were not included, 831 were not eligible for the present analysis, for the following reasons: no AMED prescription for main diagnosis at study enrolment (n = 715), disease duration <30 days (n = 45), age <1 year or >75 years (n = 19), previous participation in the AMOS study (n = 21), previous or ongoing use of AM therapy in question (n = 31). The remaining 409 patients were potentially eligible but not evaluable for the present analysis because of missing data for medication prescription at study enrolment (n = 118) or were not included in the AMOS study for the following reasons: patients' baseline questionnaire missing (n = 137), physicians' baseline questionnaire missing

(n = 40), patients' and physicians' baseline questionnaire dated >30 days apart (n = 78), no informed consent (n = 13), other reasons (n = 23).

The not-included, potentially eligible patients (NIPE, n = 409) did not differ significantly from included patients (n = 665) regarding age, gender, disease duration, baseline Disease Score or baseline Symptom Score. A main diagnosis of a mental disorder (International Classification of Diseases, Tenth Edition [ICD-10] F00-F99) was more frequent in NIPE patients (43.1%) than in included patients (30.1%) ($p < 0.001$).

A total of 66.9% (445 of 665) of patients were enrolled by general practitioners, 12.8% by pediatricians, 9.0% by internists, and 11.3% by other specialists. The physicians' settings were primary care practices (75.0% of patients, n = 499 of 665), referral practices (16.5%), and outpatient clinics (8.4%). Each physician enrolled 1–4 patients (68%, 75/110 physicians), 5–9 patients (15%) or ≥10 patients (16%), with a median of 3.0 patients per physician (range 1–45 patients, interquartile range [IQR] 1.0–6.0 patients). The last patient follow-up ensued on 5 February 2007.

A total of 93.4% (621/665) of patients returned at least one follow-up questionnaire. Follow-up rates were 90.5% (602 of 665), 84.7%, and 81.5% after 3, 6, and 12 months, respectively. Respondents and non-respondents of the six-month patient-follow-up did not differ significantly regarding age, gender, diagnosis, disease duration, baseline Disease Score or baseline Symptom Score. The physician six-month follow-up documentation was available for 92.0% (612/665) of patients.

Baseline characteristics

Disease status

Most main diagnoses belonged to the following ICD-10 chapters: F00-F99 Mental Disorders (30.1%, 200 of 665 patients), J00-J99 Respiratory Diseases (14.7%), M00-M99 Musculoskeletal Diseases (11.1%), G00-G99 Nervous System Diseases (8.0%), and N00-N99 Genitourinary Diseases (7.1%). Most common diagnosis subgroups were Asthma/Sinusitis/Bronchitis (J32, J40-J42, J44-J45: 11.1%, 74 of 665 patients), Mood Disorders (F31-F39: 9.8%), Headache (G43-G44, R51: 5.3%), and Menstruation-related Gynecological Disorders (N80, N92, N94.3-N94.6, N95: 4.7%). The disease duration was 1–2 months in 5.4% (36/662) of evaluable patients, 3–5 months in 5.9%, 6–11 months in 9.0%, and ≥12 months in 79.6%, with a median disease duration of 3.3 (IQR 1.0–10.0) years. Patients had a median of 1.0 (IQR 1.0–2.0) comorbid diseases. The most common comorbid diseases were M00-M99 Musculoskeletal Diseases (14.3%, 145 of 1,015 diagnoses), F00-F99 Mental Disorders (11.8%), J00-J99 Respiratory Diseases (11.1%), and 100–199 Cardiovascular Diseases (8.8%).

Socio-demographic data

Patients were recruited from 15 of 16 German federal states. Age groups were 1–19 years (29.9%, 199 of 665 patients), 20–39 years (25.3%), 40–59 years (34.9%), and 60–75 years (9.9%) with a median age of 37.0 years (IQR 12.9–47.5 years, mean 33.9 years, SD 19.3). A total of 68.4% (455 of 665) of patients and 79.7% (379/475) of adults were women. Compared with the German population, patients had higher educational and occupational levels and were less frequently unemployed, living alone, regular smokers, daily alcohol consumers, and overweight; socio-demographic status was similar to the population regarding low income and less favorable for work disability pension and sick-leave (Table 1).

Therapy in the first six study months

At study enrolment, the duration of the consultation with the AM physician was <30 min in 22.1% (147/665) of patients, 30–44 min in 30.4%, 45–59 min in 15.5%, and ≥60 min in 20.3% of patients. During the first six study months, use of at least one AMED product was documented for 77.6% (443 of 571) of evaluable patients. Administration frequency for AMED was daily (73.4%, 1,239 of 1,689 documentations), 3–6 days per week (8.8%), 1–2 days per week (12.1%), 1–3 days per month (2.7%), <1 day per month (0.7%), unknown (2.3%). A total of 3,930 patient-months of AMED use were documented, corresponding to a continuous use of average 1.5 AMED per patient during the six-month period. Six-hundred and fifty-two (652) different AMED were used; the origin of AMED was mineral (8.0%, 52 of 652 AMED), botanical (39.0%), zoological (7.2%), chemically defined (13.0%), and mixed (33.0%). The most common administration forms were dilutions for oral use (31.4%, 205 of 652 AMED), ampoules for injection (20.1%), globuli (19.8%), powders (10.9%), and ointments (6.9%). The most frequently used individual AMED products were Hepatodoron Tablets (used by 8.4%, 37 of 443 evaluable patients), Cardiodoron Liquid (4.5%), Abnobaviscum Ampoules (3.6%), Phosphorous Liquid (3.4%), and Ovaria comp. Globuli (2.9%).

Non-AMED products were used by 69.0% (388 of 562) of evaluable patients. In total 3,295 patient-months of non-AMED use were documented; the most frequently used Anatomical Therapeutic Chemical Classification Index groups were Nervous System (18.9%, 623 of 3,295 patient-months), Alimentary

Table 1 Socio-demographic characteristics of adult study patients

Item	Subgroup	Patients		German population	
		N	%	%	Reference
Education (Brauns and Steinmann 1997)					(Federal Statistical Office 2001)
-Low (grade 1)		83/475	17%	43%	(Anonymous 2000)
-Intermediate (grade 2)		242/475	51%	43%	
-High (grade 3)		150475	32%	14%	
Wage earners		19/475	4%	18%	(Federal Statistical Office 2001)
Unemployed during last 12 months	Economically active patients	15/277	5%	10%	(Federal Statistical Office 2001)
Living alone		91/661	14%	21%	(Federal Statistical Office 2001)
Net family income <900 € per month		64/388	16%	16%	(Federal Statistical Office 2001)
Alcohol use daily (patients) vs almost daily (Germany)	Male	9/96	9%	28%	(Hoffmeister et al 1999)
	Female	5/379	1%	11%	
Regular smoking	Male	12/96	13%	37%	(Junge and Nagel 1999)
	Female	38/378	10%	28%	
Sports activity ≥1 hour weekly	Age 25–69	206/432	48%	39%	(Breckenkamp et al 2001)
Body mass index <18.5 (low)	Male	0/94	0%	1%	(Federal Statistical Office 2001)
	Female	26/373	7%	4%	
Body mass index ≥25 (overweight)	Male	34/94	36%	56%	(Federal Statistical Office 2001)
	Female	93/373	25%	39%	
Permanent work disability pension		39/475	8%	3%	(Association of German Pension Insurance Companies 2005)
Severe disability status		47/475	10%	12%	(Bergmann and Ellert 2000)
Sick leave days in the last 12 months (mean)	Economically active patients	34.2		17.0	(Anonymous 2003)

Tract and Metabolism (14.1%), Respiratory System (10.0%), and Cardiovascular System (9.7%). AM adjunctive therapies (eurythmy, art or rhythmical massage therapy) were used by 50.0% (280 of 559) of evaluable patients.

Use of diagnosis-related non-AM adjunctive therapies within the first six study months was analyzed in patients with a main diagnosis of mental, respiratory or musculoskeletal diseases, headache syndromes or menstruation-related gynecological disorders (Table 2, n = 438). Patients were classified as users if they had used at least one of the listed therapies for at least one day per month. Out of 356 evaluable patients, 64.9% (n = 231) had no diagnosis-related adjunctive therapy.

Clinical outcomes

Disease severity

Disease and Symptom Scores (Figure 1) improved significantly and progressively between baseline and all subsequent follow-ups. After six months, an improvement of ≥30% of baseline scores was observed in 67.4% (393 of 583 evaluable patients) and 59.7% (334/559) for Disease and Symptom Scores, respectively; an improvement of ≥50% was observed in 50.0% (292/583) and 43.5% (243/559), respectively. Standardized Response Mean effect sizes for the 0–6 month comparison were large for both scores (Table 3).

Disease and Symptom Scores were analyzed in adult men and women, in children, and in the nine diagnostic subgroups listed in the 'Baseline characteristics' section. From baseline to six-month follow-up, both outcomes improved significantly in all analyzed subgroups ($p = 0.002$ for Disease Score in Malignancies; $p < 0.001$ for all other comparisons). With one exception (Symptom Score in Menstruation-related Gynecological Disorders: effect size 0.76), all effect sizes were large. Among the five most common ICD-10 chapters, effect sizes for Disease Score ranged from 1.10 (M00–M99 Musculoskeletal Disease) to 1.61 (G00–G99 Nervous System Diseases), while effect sizes for Symptom Score ranged from 0.85 (N00–N99 Genitourinary Diseases) to 1.15 (J00–J99 Respiratory Diseases). The 0–6 month improvements of Disease and Symptom Score did not correlate with education level (Spearman Rho for Disease Score $r = -0.04$, $p = 0.411$; for Symptom Score $r = 0.06$, $p = 0.212$) or duration of consultation at study enrolment (Disease Score $r = 0.04$, $p = 0.505$; Symptom Score $r = 0.00$, $p = 0.995$).

We performed five sensitivity analyses of 0–6 month Disease Score outcomes (Table 4: SA1-SA5; see Methods for further description). The individual analyses had only small effects, reducing the improvement by maximum 10%. Combining all five analyses, Disease Score improvement was reduced by 15% (3.27→2.78 points).

Table 2 Diagnosis-related adjunctive therapies

Main diagnosis (International classification of diseases, tenth edition)	Drugs (Anatomical therapeutic chemical classification index)	Non-medication therapy
Mental disorders (F00-F99)	Antiepileptic, psycholeptic, analeptic, and anti-addiction drugs (N03A, N05-06, N07B)	Psychotherapy (in children ergotherapy or play therapy)
Respiratory disorders (J00-J99)	Respiratory drugs (H02, J01-02, J04-05, J07A, L03, R01, R03, R06-07)	Relevant surgery
Musculoskeletal diseases (M00-M99)	Immunosuppressive, musculoskeletal, analgesic, and antidepressant drugs (L04, M01-05, M09, N02A-B, N06A)	Physiotherapy, relevant surgery
Headache disorders (G43-G44, R51)	Analgesics, antimigraine drugs, antidepressants (C04AX01, C07AA05, C07AB02, C08CA06, C08DA01, N02, N03AG01, N06A, N07CA03)	
Menstruation-related gynecological disorders		
-Endometriosis (N80)	Sex hormones, gonadotropin-releasing hormone analogues (G03, L02AE)	Relevant surgery
-Excessive, frequent and irregular menstruation (N92)	Sex hormones, iron preparations (G03, B03A)	Relevant surgery
-Premenstrual tension syndrome (N94.3)	Sex hormones, antidepressants, diuretics (G03, N06A, C03)	
-Dysmenorrhea (N94.4-94.6)	Sex hormones, analgesics, non-steroid anti-inflammatory drugs, muscle relaxants (G03, N02, M01A-M01B, M03)	
-Menopausal and other perimenopausal disorders (N95)	Sex hormones (G03)	

Quality of life

In adults, all eleven SF-36 scores (Figure 2) improved significantly and progressively between baseline and all subsequent follow-ups (one exception to progressive improvement: SF-36 Health Change score was unchanged from 6-month to 12-month follow-up). In children, quality of life scores improved progressively between baseline and most subsequent follow-ups (improvement at 12 out of 15 follow-ups); seven of 15 improvements were statistically significant. Effect sizes for the 0–6 month comparison were medium for five quality of life scores and small for 11 scores (Table 3).

Other outcomes

At six-month follow-up, patients' average therapy outcome rating (numeric scale from 0 "no help at all" to 10 "helped

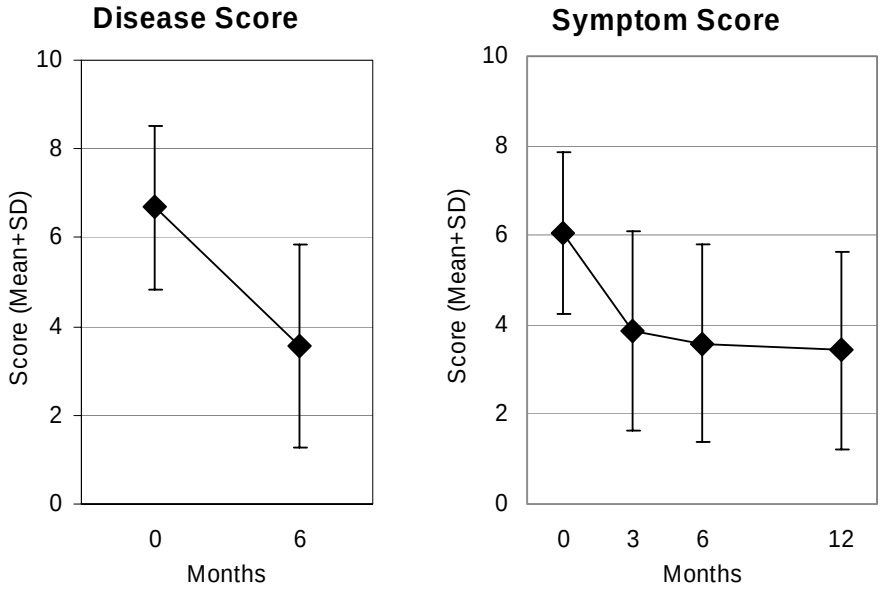

Figure 1 Disease Score (physicians' assessment), Symptom Score (patients' assessment), 0 "not present", 10 "worst possible".

Table 3 Clinical outcomes 0–6 months

Item	Age (years)	N	0 months		6 months		0–6 month difference[a]	p-value	Improved	SRM[b]
			Mean	±SD	Mean	±SD	Mean (95%-CI)			
Disease score (0–10)	1–75	583	6.71	±1.86	3.56	±2.29	3.15 (2.97–3.34)	$p < 0.001$	87%	1.35
Symptom score (0–10)	1–75	559	6.03	±1.79	3.60	±2.22	2.43 (2.23–2.63)	$p < 0.001$	82%	1.01
SF-36 scales (0–100)										
-Physical function	17–75	395	76.04	±24.43	81.08	±23.19	5.05 (3.29–6.80)	$p < 0.001$	53%	0.28
-Role physical	17–75	390	51.41	±39.70	67.23	±38.01	15.81 (12.03–19.60)	$p < 0.001$	44%	0.42
-Role-emotional	17–75	388	54.90	±41.53	70.15	±38.68	15.25 (10.86–19.64	$p < 0.001$	37%	0.35
-Social functioning	17–75	398	61.59	±26.36	74.69	±25.47	13.10 (10.62–15.57)	$p < 0.001$	58%	0.52
-Mental health	17–75	398	56.60	±19.80	65.55	±17.69	8.95 (7.29–10.61)	$p < 0.001$	65%	0.53
-Bodily pain	17–75	398	56.24	±29.41	67.30	±28.50	11.06 (8.47–13.64)	$p < 0.001$	58%	0.38
-Vitality	17–75	398	40.88	±19.38	51.41	±18.38	10.53 (8.75–12.31)	$p < 0.001$	66%	0.58
-General health	17–75	387	52.15	±19.76	58.18	±20.35	6.04 (4.48–4.60)	$p < 0.001$	60%	0.39
SF-36 Health change (1–5[c])	17–75	396	3.54	±0.80	3.17	±0.75	0.37 (0.29–0.45)	$p < 0.001$	40%	0.47
SF-36 Physical component	17–75	378	43.83	±10.84	46.87	±10.45	3.04 (2.16–3.91)	$p < 0.001$	66%	0.35
SF-36 Mental component	17–75	378	39.48	±12.52	45.23	±11.26	5.75 (4.59–6.92)	$p < 0.001$	71%	0.50
KINDL 40-item, total[d]	8–16	25	66.74	±12.67	73.44	±10.49	6.69 (1.95–11.44)	$p = 0.008$	84%	0.58
KINDL (Kid or Kiddo) total[e]	8–16	53	69.64	±14.61	72.78	±11.01	3.14 (–0.14 to 6.42)	$p = 0.060$	64%	0.26
KITA daily life[d]	1–7	26	61.22	±16.70	66.67	±17.87	5.45 (–2.64 to 13.54)	$p = 0.178$	50%	0.27
KITA psychosoma[d]	1–7	24	69.62	±15.11	75.09	±17.66	5.47 (–1.53 to 12.47)	$p = 0.120$	50%	0.33
KINDL (Kiddy) total[e]	4–7	42	66.08	±10.59	69.54	±10.67	2.80 (0.11–5.50)	$p = 0.042$	62%	0.35

[a]Positive differences indicate improvement. Improved: Percentage of patients improved from baseline.
[b]SRM: Standardized Response Mean effect size (small: 0.20–0.49, medium: 0.50–0.79, large: ≥0.80)
[c]1 = "much better now than one year ago", 5 = "much worse now than one year ago".
[d]Patients enrolled up till 31 March 2001
[e]Patients enrolled 1 April 2001 and thereafter

Table 4 Disease Score 0–6 months: Sensitivity analysis (SA)

Item	N	0 months		6 months		0–6 month difference	
		Mean	±SD	Mean	±SD	Mean (95%-CI)	p-value
Main analysis: patients with evaluable Disease Score at 0 and 6 months	583	6.71	±1.86	3.56	±2.29	3.15 (2.97–3.34)	$p < 0.001$
SA1: Patients with 6-month patient-follow-up questionnaire available	503	6.71	±1.88	3.58	±2.28	3.14 (2.93–3.34)	$p < 0.001$
SA2: Baseline value carried forward	560	6.69	±1.87	3.87	±2.39	2.82 (2.62–3.02)	$p < 0.001$
SA3: Patients not using eurythmy or art therapy or rhythmical massage therapy in month 0–6	250	6.39	±1.95	3.17	±2.12	3.22 (2.93–3.51)	$p < 0.001$
SA4: Patients with disease duration ≥12 months at study enrolment	401	6.81	±1.86	3.74	±2.29	3.06 (2.83–3.29)	$p < 0.001$
SA1 + SA2 + SA3 + SA4 Patients with main diagnosis of musculoskeletal or mental diseases, headache disorders, or menstruation-related gynecological disorders	220	6.52	±1.91	3.70	±2.34	2.83 (2.50–3.15)	$p < 0.001$
Main analysis: patients with evaluable Disease Score at 0 and 6 months	392	6.66	±1.78	3.39	±2.18	3.27 (3.04–3.49)	$p < 0.001$
SA 1: Patients with 6-month patient-follow-up questionnaire available	331	6.66	±1.79	3.45	±2.17	3.20 (2.96–3.44)	$p < 0.001$
SA5: Patients not using diagnosis-related adjunctive therapies (see text) in month 0–6	208	6.54	±1.82	3.24	±2.16	3.30 (2.98–3.62)	$p < 0.001$
SA1 + SA2 + SA3 + SA4 + SA5	94	5.98	±1.82	3.20	±2.19	2.78 (2.32–3.23)	$p < 0.001$

very well") was 7.12 ± 2.46; patient satisfaction with therapy (from 0 "very dissatisfied" to 10 "very satisfied") was 7.80 ± 2.26. Ratings of therapy outcome and satisfaction did not differ significantly between adults (patient rating) and children (proxy rating by caregivers). From 6- to 12-month follow-up, patient satisfaction decreased by average 0.24 points, 95% CI 0.03–0.45, p = 0.024, whereas patients' therapy outcome rating did not change significantly.

Adverse drug reactions were reported significantly less frequently from AMED than from non-AMED products (Table 5).

Serious adverse events were documented in 12 patients. Six patients died from a malignant disease (cervical carcinoma in two patients, four different malignancies in remaining four patients) that had been present at study enrolment. One patient suffered a whiplash injury with permanent disability.

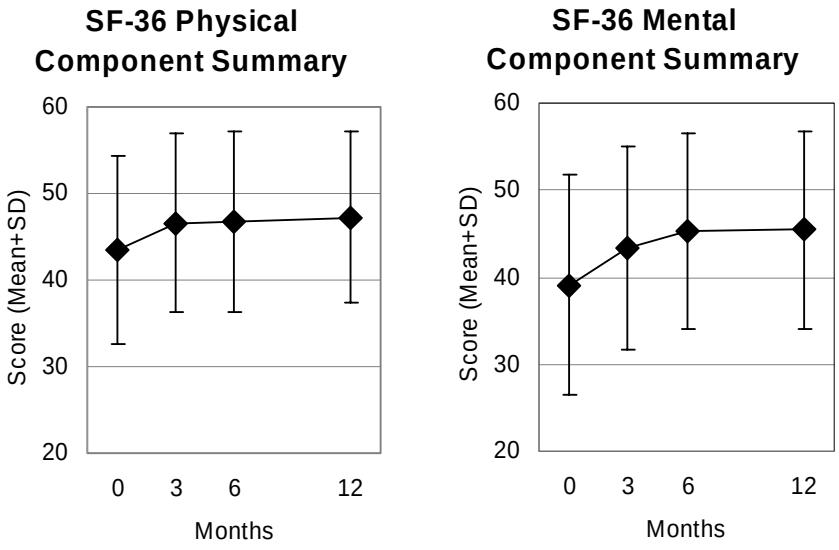

Figure 2 SF-36 Physical and Mental Component Summary Measures. Higher scores indicate better health. Adult patients.

Table 5 Adverse drug reactions reported from anthroposophic (AMED) and other (non-AMED) medications during the 12-month follow-up

	AMED n = 478 users		**Non-AMED n = 465 users**		
Adverse drug reaction	N	%	N	%	p-value
-any	25	5.2%	42	9.0%	p = 0.031
-of severe intensity	6	1.3%	15	3.2%	p = 0.047
-leading to discontinuation of medication use	14	2.9%	22	4.7%	p = 0.175

Five patients were acutely hospitalized: two patients for exacerbation of paranoid schizophrenia; remaining three patients for thrombosis of lower extremity, intestinal perforation from swallowing fish bones, and life-threatening adhesive ileus, respectively. The patients with thrombosis and ileus had sequelae; the other acutely hospitalized patients recovered completely. None of these serious adverse events were causally related to any medication or therapy.

Discussion

This prospective cohort study is the first study of individualized AMED therapy for chronic disease performed in office-based settings. We aimed to obtain information on AMED therapy under routine conditions in Germany and studied clinical outcomes in outpatients with a new prescription of AMED for chronic diseases. Most frequent indications were mental, respiratory, musculoskeletal, neurological, and genitourinary disorders.

Following AMED therapy, significant improvements of disease symptoms and quality of life were observed.

Strengths of this study include a long follow-up period, high follow-up rates for the physician documentation, and the participation of 28% of all AM-certified physicians in Germany. The participating physicians resembled eligible but not participating physicians with respect to demographic characteristics, and the included patients resembled not included, potentially eligible patients regarding baseline characteristics. These features suggest that the study to a high degree mirrors contemporary AMED therapy in outpatient settings.

On the other hand, it was not feasible to have disease-specific outcomes for all diagnoses included. Nonetheless, the larger AMOS project, of which this study is part, included disease-specific outcomes for major disease groups (Hamre et al 2006a, 2007b).

Since the study had a long recruitment period, the study physicians were not able to participate throughout the period and to screen and enroll all eligible patients (criteria: see Methods section). For patients referred to AM therapies and enrolled before 1 April 2001, it was estimated that physicians enrolled every fourth eligible patient (Hamre et al 2006a). This selection could bias results if physicians were able to predict therapy response and if they preferentially screened and enrolled such patients for whom they expected a particularly favorable outcome. In this case one would expect the degree of selection (= the proportion of eligible vs enrolled patients) to correlate positively with clinical outcomes. That was not the case, the correlation was almost zero (–0.04). This analysis (Hamre et al 2006a) does not suggest that physicians' screening of eligible patients was affected by selection bias. – Among screened patients who were potentially eligible, 38% could not be included in the analysis (NIPE-patients), mostly because of missing baseline data. NIPE patients did not differ from included patients regarding demographics, disease severity or disease duration, but a main diagnosis of mental disorders was more frequent among NIPE patients (43% vs 30%), so a selection bias affecting the diagnosis distribution cannot be ruled out.

Since 18 clinical outcomes were analyzed, the issue of multiple hypothesis-testing arises (Feise 2002). However, 15 of 18 analyzed 0–6 month comparisons of clinical outcomes showed significant improvements, with $p < 0.001$ for 13 outcomes (Table 3).

A limitation of the study is the absence of a comparison group receiving another treatment or no therapy. Accordingly, for the observed improvements one has to consider several other causes apart from AMED. In a sensitivity analysis of Disease Score, attrition bias, adjunctive therapies, and natural recovery could together explain only up to 15% of the improvement. According to an analysis published elsewhere (Hamre et al 2007a), regression to the mean due to symptom fluctuation with preferential self-selection to therapy and study inclusion at symptom peaks could explain additionally 0.43 points of the Disease Score improvement, resulting in a minimum unexplained improvement of average 2.35 points (lower boundary of 95% CI 1.89 points). Other possible confounders are psychological factors like patient expectations. Since, however, AMED therapy was evaluated as a whole system, the question of specific therapy effects vs nonspecific effects (placebo effects, context effects,

physician-patient interactions, patient expectations etc) was not an issue of the present analysis.

Since patients were treated by AM physicians who could possibly have an interest in AMED therapy having favorable outcomes, study data were largely collected by patients and not physicians. Any bias affecting physician's documentation would not affect Symptom Score or quality of life, since these clinical outcomes were documented by the patients or caregivers.

Medication and therapy use was documented by the patients at each follow-up and patients may have forgotten some medications and therapies, leading to an underestimation of true use (Evans and Crawford 1999). Therefore, the proportion of patients using AMED – or using adjunctive therapies (sensitivity analyses SA3 and SA5) – might be higher than documented. Since SA3 and SA5 did not decrease the Disease Score improvement, a higher proportion of adjunctive therapy users would not be expected to reverse these results and would thus not threaten the validity of these analyses.

This study confirms previous studies of AM users (Ritchie et al 2001; Pampallona et al 2002; Hamre et al 2005; Unkelbach and Abholz 2006): Patients are predominantly women or children; education and occupation levels are higher than average, and typical indications are mental, respiratory, and musculoskeletal disorders. Up till now AMED therapy for chronic noncancer indications has been evaluated in 52 studies. 51 studies showed some benefit; one study found no benefit (Kienle et al 2006a). Most studies concerned single AMED products (29 studies) or a fixed AMED combination (16 studies). Seven studies evaluated individualized AMED therapy in combination with nonmedication AM therapies for epilepsy (Madeleyn 1990), sciatica (Kienle et al 2006c), atopic diseases (Knol 1989; Kienle et al 2006b), anorexia nervosa (Schmitz 1989; Kienle et al 2006d), and inflammatory rheumatic disorders (Simon et al 1997), respectively. These studies were performed in inpatient hospitals (Knol 1989; Schmitz 1989; Kienle et al 2006c, 2006d) or outpatient clinics (Madeleyn 1990; Simon et al 1997; Kienle et al 2006b).

In accordance with these studies from secondary care, our study from a predominantly primary care setting showed significant improvements of mental, respiratory, musculoskeletal, neurological, genitourinary and other chronic diseases following individualized AMED therapy. The largest improvements (large effect sizes, half of patients improved by at least 50% of their baseline scores) were observed for the items which directly measure the conditions treated with AMED products, ie, Disease and Symptom Scores. Quality of life improvements were less outspoken and not significant in some of the smaller subgroups analyzed (KINDL, KITA in children). However, a comparative analysis of a larger dataset from the AMOS study shows that quality of life improvements in adults (SF-36) are a largely of the same order of magnitude as corresponding improvements following other treatments for the same diseases (Hamre et al manuscript submitted).

Conclusion

In this study, outpatients using AMED for mental, respiratory, musculoskeletal, neurological, genitourinary, and other chronic diseases had long-term reduction of disease severity and improvement of quality of life. Improvements were similar in patients not using adjunctive therapies and in patients with long disease duration. Although the pre-post design of the present study does not allow for conclusions about comparative effectiveness, study findings suggest that AMED may play a beneficial role in the long-term care of patients with chronic diseases.

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