ORIGINAL ARTICLE

Treatment of patients burdened with lipophilic toxicants: A randomized controlled trial

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Submitted: 2009-10-01 Accepted: 2009-10-20 Published online: 2009-12-25

Key words: **environmentally related diseases; detoxification; quality of life; neuropsychological achievement; lipophilic toxic compounds**

Act Nerv Super Rediviva 2009; **51**(3-4): 133–141 ANSR51349A02 © 2009 Act Nerv Super Rediviva

Abstract

OBJECTIVE*:* Currently available medical treatment options for patients with environmentally related diseases and objective toxic burden have not been shown to be effective in therapeutic studies according to stringent methodological criteria.
DESIGN*:* Randomized controlled trial. Patients were randomized into three groups: the "experimental treatment group" (EG) receiving a complex and intensive therapy protocol, the "control treatment group" (CG) receiving similar treatment with modified intensity and placebo wherever possible, the "waiting group" (WG) with no treatment.
PARTICIPANTS*:* 36 outpatients with defined toxic burden below NOAEL levels and multiple complaints, but no psychotizism or hypochondrizism.
EVALUATION/MEASUREMENTS*:* Outcome parameters included psychic and somatic variables related to psychological well-being, neuropsychological abilitiy and serum concentrations of selected persistent organochlorides.
RESULTS*:* Treatment effects were generally seen in psychological and neuropsychological tests between EG to WG. Differences were significant in most psychological life quality parameters. Patients of EG described less complaints after the treatment than those of CG. Further positive effects were observed in time-dependent cognitive measurements (ZVT, d2, WL-G). Biomonitoring parameters did not indicate any changes in toxic burden.
CONCLUSION AND RELEVANCE TO CLINICAL PRACTICE*:* Our data indicate support for the efficacy of the complex therapy for affected patients. The lack of correlation between psychological and neuropsychological improvement and body burdens needs further studies.

Acknowledgements
The study was supported by a grant from the Federal Ministry of Health and Social Security (BMGS), Germany (AZ 122-1720/48).

Declaration
This study was performed in accordance with all national and institutional guidelines for the protection of human welfare in therapeutic interventional studies.

Introduction

Environmentally related diseases like "sick building syndrome" (SBS) or "multiple chemical sensitivity" (MCS) have captured increased attention during the last 25 years (Ohnsorge 2001). The discussion of adequate treatment options for these patients currently is controversial. One option places major emphasis on different patient perception of environmentally diseases, with focus on patient situations; the other side underscores somatic reaction to toxic burdens mainly from toxicology, occupational medicine or hygiene. Research usually has followed a dose effect relationship resulting in defining maximum exposure levels (NOAEL, no observed adverse effect levels) regarded as nontoxic to normal human beings. Organic and psychological effects in individuals exposed below these limits are mostly interpreted as psychosomatic reactions not induced by toxicants at subthreshold levels. Treatment of patients with environmentally related diseases has been dominated by this approach.

Explanation in environmental medicine focuses on the individual toxic burden. Consequently, individual patient treatment combines different etiological parameters. A complex multifaceted, toxicant induced disease process is seen as causal in patients with special susceptibility to chemicals. The daily practice of environmental diseases practitioners is based on this second interpretation both in diagnosis and therapy.

Naturally treatment options have to differ depending on these two possible explanations, neither of which has been proven yet. Whereas avoidance of toxic compounds and detoxification are generally accepted (comparable to allergic compounds), additional options like optimized nutrition (Ross 1992), continuous or discontinuous confrontation with or desensitization against toxicants (Bock & Birbaumer 1998) have been proposed. Other treatments are aimed at improving individual symptoms. Some authors (e.g. Levine & Reinhardt 1983) assume increased sensitivity to environmental compounds if the normal defence against free radicals breaks down due to e.g. exposition or infections. Consequently they recommend antioxidant supplementation.

Due to their high lipophily and persistence polychlorinated biphenyls (PCB), hexachlorobenzene (HCB) and DDT as well as its breakdown products like p-dichlorodiphenylethylene (DDE) are detectable in serum and body fat of nearly every human being. Decreasing this burden is assumed to be a valid treatment option. These compounds slowly accumulate in fat tissue, for excretion they have to be mobilized from their depots. This may be induced by e.g. therapeutic sauna or "fever bank" treatment combined with a physical training program increasing fat turnover. Reducing the body burden by this approach has been shown by some authors (Roehm 1983; Tretjak *et al* 1990); however, no corroborative proof from other groups has been published. Sweat excretion of these toxicants induced by thermal treatment (Wolff *et al* 1982), massage and lymph drainage also have been postulated to be effective (Adcock 1987). Detoxification therapy has been shown to improve symptoms in burdened patients (Kilburn 1989; Rea *et al* 1991).

To detoxify free radicals from xenobiotic metabolism antioxidant supplementation has been promoted, e.g. vitamins B_1, B_2, B_3, B_6, B_{12}, C or E (Clarkson & Thompson 2000; Kelly 1998). Similarly, excretion of toxic compounds has been attributed to vasodilatative effects e.g. of niacin (vitamin B_3; Fuccella *et al* 1980). Galland (1987) reports an improvement of 25% in clinical scores by treating chemically sensitive patients with the trace elements selen and zinc. Older studies found symptom improvement in environmentally burdened patients by detoxification therapies (Kilburn 1989; Rea *et al* 1991); however, these studies have not been reproduced.

None of the studies mentioned above controlled the efficacy of single elements in complex therapies. There is no study performed as randomized controlled trial. Therefore the effectiveness of complex treatment schedules for patients with increased sensitivity to toxicants yet has not been demonstrated.

The objective of this randomized controlled trial is to investigate whether a complex therapy consisting of physical treatment, decreased oxidative damage by vitamin and trace element supplementation and supportive detoxification can improve symptoms presented by burdened patients. Special emphasis is placed on the patient self assessment of feeling and emotional state as outcome parameters.

Materials and Methods

Experimental design and patients

The study was based on a randomization design with three independent groups: experimental treatment group (EG), control treatment group (CG), waiting group (WG, see interventional protocol). 36 Patients were enrolled in the trial, each group consisted of 12 patients. Approval from the Ethics Committee (Bayerische Landesärztekammer = Bavarian State Physicians Chamber) and written consent from the patients were obtained. Patients were recruited from the outpatient pool of one of the authors (P.O.).

Inclusion criteria

- Existing body burden by toxicants: increased serum levels in at least one of the following toxicants: PCB 138 > 500 ng/l, PCB 153 > 600 ng/l, PCB 180 > 130 ng/l, HCB > 1 000 ng/l, sum of DDT and DDE > 2 300 ng/l. The threshold values are higher than the 95th percentile of all samples analyzed in the analytical laboratory (Bauer Laboratories, PD Dr.med. K. Bauer, Berliner Promenade 70, D-66111 Saarbrücken).

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Table 1: Therapy elements in the treatment groups

Treatment	Experimental treatment group	Control treatment group
heat treatment	• Sauna at 65°C and 70% humidity for 15 min, including intense brushing; • Fever bank with increase in core temperature by 1-1.5°C, maximum 38.5°C (45 min); • hot showers.	• Sauna at 50°C and 30% humidity for 15 min, no brushing; • Fever bank; maintenance of core temperature; no increase or less than 0.3°C increase in core temperature (45 min); • warm showers.
physio-therapy	• exhausting physical exercise on bicycle ergometer at the upper limit of continuous aerobic exercise (15 min); • cold water application on lower extremities; • lymph drainage; • lymph drainage, lower extremities; • abdominal colon massage; • liver; loam bandages.	• Physical exercise on bicycle ergometer, 20% below upper limit of continuous aerobic exercise (15 min); • warm water application (37°C); • low pressure massage; • whole body placebo massage; • abdominal low pressure massage; • blanket wrapping.
detoxification treatment	• 50 mg niacin; 2 ml Na_2Se containing 100 µg Se; • 250 mg vitamin C in water/bicarbonat solution, tea and water ad lib.; • Infusion of 3 g vitamin C (4 ampoules Pascoe 750) in 250 ml NaCl solution; 98.6 mg Mg (1 amp. magnesium - 5 sulfat 10%) in 100 ml NaCl; 11 mg vitamin B1, 5 mg vitamin B2, 4 mg vitamin B6, 45 mg nicotinamide (1 amp. Lichtenstein B.complex) in 250 ml NaCl; • 100 µg Se (2 ml Na2Se) + 1 100 IE vitamin E (1/2 teaspoon); • 5 mg folic acid (folic acid Pascoe) plus 500 mg dexpanthenol (Panthenol Jenapharm) in 250 ml NaCl; additionally 1 mg cyanocobalamin (B12 Lichtenstein) plus 1 g calcium (1 amp. = 10 ml Calcium Braun, 10%) + 10 mg zinc (Zink-Injekt) in 100 ml NaCl	• placebo (rice starch plus mannit-aerosil) • tea and water ad lib. • 500 mg NaCl solution • placebo (rice starch plus mannit-aerosil) • 500 ml NaCl solution
psychological treatment	• progressive muscle relaxation according to Jacobson, relaxation with music	• relaxation with music, no muscle relaxation

- Nonspecific symptoms: symptoms are caused by at least 2 different chemicals at concentrations considered nontoxic for the general population; level 3–5 for symptoms in the MCS questionnaire (List 1, range 0–5; Hüppe *et al* 2000).
- Documented persistent sensitivity to toxicants: symptoms in at least two organ systems according to the MCS questionnaire (range 4–5 in MCS questionnaire list 2, range 0–5; Hüppe *et al* 2000) for a minimum of two years.
- Prior unsuccessful attempts to minimize exposure after diagnosis had to be documented, e.g. change of employment, household sanitization.

Exclusion criteria

- Diagnosis of psychosomatic or psychiatric disease: high level of psychoticism with a T score of >70 on the psychoticism scale of the SCL-90-R (Degoratis, German Version, Franke, 1995). Hypochondric symptoms operationalized by a Whiteley score of >9, or a score of >7 plus "yes" in item 6, or preexisting psychiatric disorder (Rief *et al* 1994)
- Preexisting somatic disease like multiple sclerosis, cancer, severe heart or circulatory disease, skin disease, lung disease including steroid dependent asthma bronchiale.

Intervention protocol

Intervention consisted of a weekly schedule with 3 active days – Monday, Wednesday, Friday – containing exhaustive physical exercise, hyperthermia (sauna or "fever bank"), massage, lymph drainage, relaxation therapy and vitamin and mineral supplementation. On passive days – Tuesday and Thursday – intensive psychic and somatic relaxation exercises like progressive muscle relaxation according to Jacobson, breathing therapy, liver and loam compresses were performed. Daily treatment lasted for 5–6 hours, the length was identical for both EG and CG groups.

The three arms were:

Experimental treatment group (EG): Patients were treated for four weeks, with daily treatment schedules for 5–6 hours, consisting of heat treatment,

physiotherapy, relaxation treatment and drug and dietary supplementation (for details see ***Table 1***). For these patients the multifactorial treatment included specific physical treatment procedures and a complete supplementation regime.

Control treatment group (CG): Patients were treated in an identical schedule as above, but specific physical treatment procedures were exchanged with non-specific physical treatment.

Medication was given only by NaCl – infusion and placebo with omission of supplements (for details see ***Table I***).

Comparison of EG and CG should allow to test the effects of specific physical treatment and separate the mere time spent in the treatment unit from effects exerted by procedures, especially the specific attention time by the therapist alone, which was kept identical in both groups.

Waiting group (WG): patients in the waiting group did not receive treatment.

Treatment was performed in a specially equipped "environmental unit" built to minimize additional exposition to toxic compounds. All furniture and cleaning material were selected for minimal toxic burden. The unit received clean air ventilation by removing dust and volatile compounds, with a four- to six fold air turnover per hour.

Patient assessment

All patients were assessed for subjective well being, neuropsychological and somatic parameters before treatment (first time of measurement: T1), one week after intervention (time point T2, reaction level 1) and five weeks after termination of the intervention (time point T3, reaction level 2). All patient assessments were performed blind. i.e. the assessor (psychologist) was unaware of the patient group, and recorded the data according to a patient code.

The following examinations were performed:

Measurement of **psychometric variables** was done by three validated questionnaires for the assessment of subjective complaints, depression and health related "Quality of Life". To assess subjective complaints the Complaint-List ("Beschwerden-Liste" B-L by von Zerssen 1976) was used. This is a 24 item questionnaire designed to quantify subjective complaints, especially for somatic symptoms. Actual depression scores were obtained by the general depression scale ADS-L ("Allgemeine Depressions Skala", Hautzinger & Bailer 1993), a 20 item self assessment and screening questionnaire to quantify depressive mood. The ADS is the German form of the widely used "Centre for Epidemiological Studies Depression Scale" (CES-D). The 36 item "Quality of Life" – questionnaire SF-36 (German form by Bullinger & Kirchberger 1998) was used to quantify eight dimensions of subjective health: physical functioning, physical role, pain, general health perception, vitality, social functioning, emotional role functioning and mental health, as well as recent health changes. Two global scores describe physical and mental health. High scores in subtests of the SF-36 indicate good quality of life.

Neuropsychological assessment was performed by tests for information processing speed, concentration and memory. The general rate of information processing was assessed by a German Trail-Making Test (known in German as Zahlenverbindungstest [ZVT], Oswald & Roth 1997). This test demands to connect the numbers 1 to 90 as fast as possible by line drawing. The necessary time in seconds was used as test score. Concentration was measured by the attention test d2 (Brickenkamp 1994) with marking of defined symbols in a list with distractors. It measures general attention and concentration capabilities. Scores included the error-corrected general score GZ-F and the concentration score KLW. Memory ability was verified using word lists for assessing 2 different aspects: "power level" (known in German as " Wortliste Niveau" [WL-N]) and "speed" (known in German as "Wortliste Geschwindigkeit [WL-G]) (Hüppe 1998). The patients were required to reproduce 10 previously read words either without a time restriction (WL-N) or with a restriction of 10 seconds (WL-G). The memory scores were determined by the number of reproduced words.

Somatic variables. To quantify toxic burden serum levels of the PCB congeners 138, 153 and 180, HCB, DDT and DDE were determined by established methods in a certified laboratory (Bauer laboratory, PD Dr. med. K. Bauer, Berliner Promenade 70, D-66111 Saarbrücken).

Statistical analysis

Statistical analysis was performed for each variable by analysis of variances with repeated measurements (MANOVA) using the factors "group" and "time point". The extend of effect differences between groups was calculated by the effect size formula of Cohen (1988). The "Effect Size" (d) is defined by the arithmetic difference of two group means related to the pooled standard deviation. The combined scores of the time points T2 and T3 were used for this analysis; patient state prior to therapy was excluded by regression statistics.

$P \leq 0.05$ was considered statistically significant, $p \leq 0.10$ significant in tendency. Due to the multiple comparisons without alpha-adjustment the results are considered mainly as exploratory (Abt 1987; 1989).

All statistical analyses were performed with the computer program SPSS for Windows (SPSS version 9.0, SPSS inc., Chicago, Illinois).

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Table 2: Results from self assessment questionnaires

Questionnaire and Variable		time	Experimental treatment group	Control treatment group	Waiting group	Analysis of variance with repeated measurement		
			M (SD)	M (SD)	M (SD)	factor	F	P
Symptom Complaint List (B-L)	Total score	BT	34.67 (13.03)	35.42 (12.59)	30.50 (12.67)	G	0.45	0.64
		RL 1	28.67 (13.05)	33.58 (11.80)	34.70 (13.78)	T	0.57	0.57
		RL 2	27.25 (13.38)	35.25 (12.23)	34.17 (12.57)	GxT	3.59	0.01 **
General Depression Scale (ADS)	Total score	BT	17.33 (9.78)	13.50 (6.88)	18.17 (7.94)	G	1.30	0.29
		RL 1	12.58 (10.53)	11.17 (7.76)	19.33 (10.59)	T	1.99	0.14
		RL 2	13.50 (9.04)	14.83 (7.92)	17.33 (7.58)	GxT	2.67	0.04 *
Health-related Quality of Life (SF-36)	Physical functioning	BT	70.42 (26.75)	60.00 (27.72)	50.00 (24.59)	G	2.83	0.07 (*)
		RL 1	67.50 (23.98)	67.50 (26.93)	47.50 (23.69)	T	1.43	0.25
		RL 2	74.17 (23.82)	69.17 (25.66)	49.58 (21.79)	GxT	1.05	0.39
	Role-physical index	BT	33.33 (37.44)	41.67 (43.08)	50.00 (39.89)	G	0.05	0.95
		RL 1	50.00 (39.93)	39.58 (43.25)	29.17 (38.19)	T	0.11	0.89
		RL 2	43.75 (37.12)	37.50 (40.59)	35.42 (41.91)	GxT	1.66	0.17
	Bodily pain	BT	59.38 (33.63)	53.08 (24.41)	45.08 (20.74)	G	0.85	0.44
		RL 1	56.13 (30.76)	51.13 (25.39)	48.75 (23.41)	T	0.14	0.86
		RL 2	60.25 (36.52)	58.04 (27.75)	42.96 (23.76)	GxT	0.66	0.61
	General health perception	BT	50.25 (18.02)	50.03 (18.43)	41.75 (15.55)	G	2.17	0.13
		RL 1	60.08 (23.83)	56.00 (21.75)	41.83 (18.18)	T	5.49	0.008 **
		RL 2	57.58 (24.15)	60.33 (20.62)	43.25 (13.27)	GxT	1.47	0.23
	Vitality	BT	35.83 (16.49)	41.67 (16.14)	41.67 (19.23)	G	0.68	0.52
		RL 1	44.58 (17.90)	47.92 (17.51)	38.75 (17.47)	T	5.93	0.007 **
		RL 2	52.92 (18.27)	52.08 (19.48)	39.17 (17.03)	GxT	2.89	0.04 *
	Social functioning	BT	63.54 (22.27)	62.50 (19.22)	68.75 (25.28)	G	0.21	0.82
		RL 1	68.75 (30.39)	66.67 (20.87)	68.75 (24.71)	T	0.94	0.40
		RL 2	75.00 (27.70)	63.54 (25.82)	69.79 (21.62)	GxT	0.65	0.63
	Role-emotional index	BT	41.67 (37.94)	69.44 (41.34)	69.44 (43.71)	G	0.02	0.98
		RL 1	66.67 (42.64)	58.33 (47.41)	47.22 (48.11)	T	0.05	0.95
		RL 2	63.89 (41.34)	52.78 (48.11)	58.33 (51.49)	GxT	1.62	0.18
	Mental health index	BT	54.67 (15.19)	58.33 (14.11)	61.67 (18.56)	G	0.02	0.98
		RL 1	66.67 (19.62)	64.33 (17.01)	56.67 (13.73)	T	0.05	0.95
		RL 2	66.76 (17.83)	63.33 (13.84)	54.33 (12.12)	GxT	1.62	0.18

Abbreviations: G: Factor «group»; T: Factor «time»; GxT: Interaction group x time
BT: before therapy; RL 1: reaction level 1 - first week after therapy; RL 2: reaction level 2 – five weeks after therapy
(*): $p < 0.10$; *: $p < 0.05$; **: $p < 0.01$; *** $p < 0.001$

Results

Patients' age ranged between 42 and 64 years (M = 56.2; SD = 6.2). Most of them were married (69.4%) or divorced/living separated (16.7%). 47.2% had a lower educational degree, 33.3% a "Realschulabschluss", equivalent to a high school degree. The three groups were also comparable in psychological parameters, i.e. extraversion and emotional stability (Freiburg Personality Inventory, Fahrenberg *et al* 1994), stress coping (Stress Coping Inventory SVF-120, Janke & Erdmann 1997), Symptom Check List SCL-90 (Franke 1995) and hypochondricity (Whiteley index; Rief *et al* 1994).

Self assessment parameters

Table 2 compiles the results from self assessment questionnaires. For the subscale "vitality" in the SF 36, as well as for the "Depression Scale" and the "Complaint-List" the interaction "group x time" showed significant results. Compared to the pre-treatment state patients in EG showed lasting improvement (decrease in symptoms and depressive mood, increase in vitality), whereas CG indicated improvement directly after treatment termination, but no lasting effects in depressive mood and symptoms. As expected, the WG was constant over time with a slight tendency to worsen. The main effect over time for general health perception depended on improvement from values prior to therapy (M=47.36, SD = 17.35) to scores one week after therapy (M =52.64, SD = 22.22, p=0.03) and four weeks later (M=53.72 , SD = 20.74, p=0.007).

Analysis of covariances using initial values as covariate yielded significance for complaint list variables immediately after treatment ($F = 3.78$; $p = 0.034$) as well as for the assessment four weeks later ($F = 5.06$; $p = 0.012$, ***Figure 1***). When both measurements after the treatment were combined to a post-treatment reaction, analysis of covariance resulted in an even higher

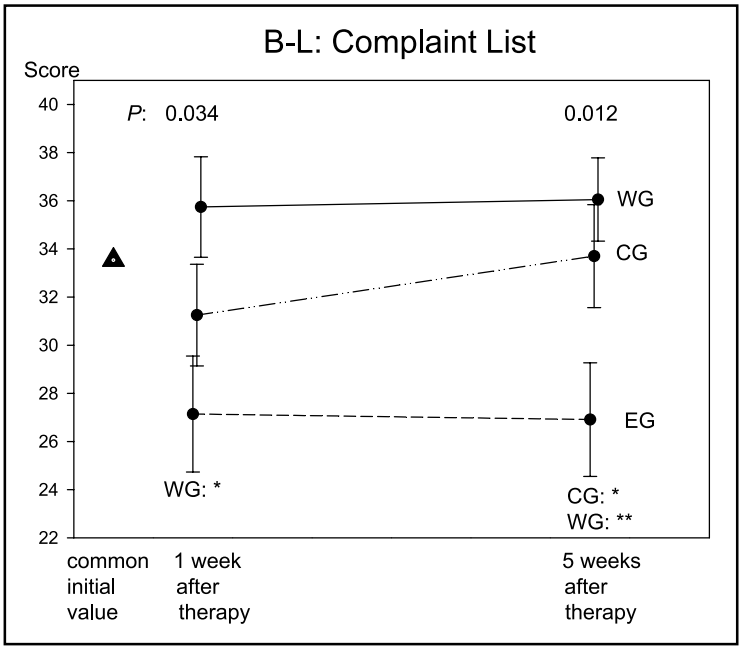

Figure 1: Group differences in the complaint list
Group differences in the complaint list controlling for pre treatment values. The numbers represent adjusted means ± SEM at the indicated time points following therapy. P-values by ANCOVA are given at the top of each time point.
Significant differences between patients in the EG are given at the bottom; *: p<0.05; **: p<0.01.
(EG: experimental treatment group; CG. Control treatment group; WG: waiting group)

Table 3: Human bio monitoring for persistent organochlorine compounds

		Experimental treatment group	Control treatment group	Waiting group	Analysis of variance with repeated measurement		
Variable	time	M (SD)	M (SD)	M (SD)	factor	F	P
PCB 138 (ng/l)	BT	750.3 (338.8)	644.0 (163.2)	899.2 (663.9)	G	0.84	0.44
	RL 1	811.1 (225.7)	673.6 (213.5)	813.2 (493.8)	T	0.97	0.36
	RL 2	895.6 (225.9)	745.7 (200.7)	859.3 (430.3)	G x T	1.12	0.36
PCB 153 (ng/l)	BT	1130.0 (544.7)	1073.7 (256.1)	1314.1 (767.2)	G	0.55	0.58
	RL 1	1188.6 (407.7)	1018.8 (190.8)	1187.2 (584.7)	T	0.60	0.55
	RL 2	1214.0 (460.8)	1086.9 (223.8)	1186.9 (535.7)	G x T	1.30	0.28
PCB 180 (ng/l)	BT	397.7 (210.7)	413.6 (133.3)	504.7 (325.0)	G	0.21	0.81
	RL 1	478.4 (163.0)	417.8 (68.3)	436.8 (227.5)	T	0.32	0.63
	RL 2	492.8 (156.6)	442.4 (123.0)	461.7 (239.3)	G x T	1.65	0.20
HCB (ng/l)	BT	1785.8 (984.6)	1655.0 (968.5)	1736.8 (712.8)	G	0.22	0.81
	RL 1	2018.8 (1231.1)	1889.7 (1001.1)	1624.2 (720.3)	T	0.41	0.64
	RL 2	1922.9 (1119.4)	1756.9 (1225.1)	1653.7 (687.3)	G x T	0.75	0.54
DDT (ng/l)	BT	33.11 (42.50)	30.75 (12.09)	55.00 (49.51)	G	0.08	0.92
	RL 1	51.60 (42.40)	59.71 (76.73)	41.80 (22.72)	T	0.40	0.66
	RL 2	56.17 (67.13)	36.29 (22.54)	51.88 (30.88)	G x T	0.82	0.52
DDE (ng/l)	BT	4943.3 (7345.7)	2182.5 (1125.8)	3290.8 (2537.3)	G	0.64	0.54
	RL 1	5233.4 (7580.6)	2234.8 (999.1)	3640.8 (2511.6)	T	0.63	0.46
	RL 2	6436.1 (11066)	2511.4 (1898.4)	3471.8 (2597.3)	G x T	0.75	0.50

Abbreviations: G: Factor «group»; T: Factor «time»; GxT: Interaction group x time
BT: before therapy; RL 1: reaction level 1 - first week after therapy; RL 2: reaction level 2 – five weeks after therapy

group difference (F = 5.56; .p= 0.008). The EG had the least symptoms (M = 27.63, SD = 6.58), and the WG the highest scores (M = 36.26, SD = 5.82); Values for the CG were in between as might be expected (M = 32.95 SD = 6.56). The Duncan post hoc test showed significant differences between EG and WG ($p < 0.01$) and between EG and CG ($p < 0.05$); no difference was seen between CG and WG ($p = 0.21$).

Neuropsychological assessment

Analysis of variance did not show any interaction between group and time of measurement ($p > 0.10$). Main effects for the factor "time" were significant for the concentration test d2 and trail tracing test ($p < 0.001$ for each variable). Performance improved considerably for both tests. Especially in the concentration index of the d2 test improvements were pronounced. No major effects could be seen for the factor "group".

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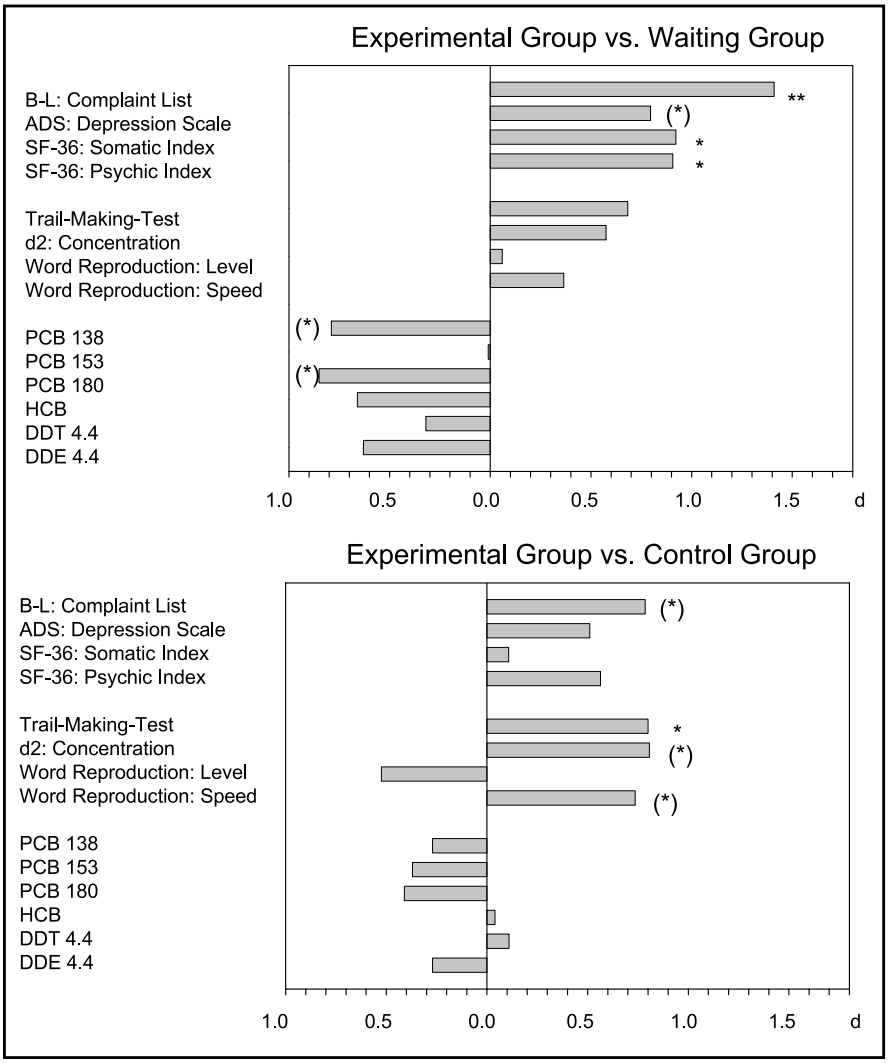

Figure 2: Group differences in effect size
Effect size is shown for differences between EG and WG (upper panel) and between EG and CG (lower panel). Bars running to the right side indicate scores in favour to the experimental treatment group, bars running to the left side indicate worse scores for the experimental treatment group.
(*): p<0.10; *: p<0.05; **: p<0.01

Serum concentration in toxic compounds
Serum samples were assayed for polychlorinated biphenyls 138, 153 and 180, HCB, DDT and DDE to monitor changes in toxic burden at three time points: before, one week and five weeks after therapy. Statistical analysis indicated no significant changes in serum concentrations ($p > 0.10$ for all main effects and interactions). Values from human biomonitoring are summarized in ***Table 3***.

Effect size of the experimental treatment group
Effect sizes were calculated to compare EG with CG and EG with WG with respect to outcome measurements. Analysis was done with aggregated post treatment values using scores prior to the therapy as covariables in a statistical regression analysis. The results from EG to both CG and WG are summarized in ***Figure 2***.

Patients in the EG showed strong positive effects compared to patients in the WG especially in the self assessment parameters. Strongest effects were seen in the complaint list (B-L) with d = 1.41. Group differences in favor of EG were also seen in neuropsychological variables; however, group differences were not significant. With the exception of PCB 153 all values from human biomonitoring were higher in EG as compared to the waiting group, for PCB 138 and PCB 180 differences were even higher in tendency. The effect sizes were strong in these variables (PCB 138: d = 0.79; PCB 180: d = 0.85).

When comparing EG with CG the experimental treatment group showed better values for subjective variables. The effect size was calculated as d = 0.70 for the complaint list (B-L). Group differences for information processing speed (d = 0.80), for concentration (d2 test, d = 0.81) and for the time-limited word reproduction test (d = 0.74) indicated a similar association. However, values for word reproduction test were lower in the experimental treatment group compared to the control group (d = –0.52). Nearly all variables in human biomonitoring were higher in the EG as compared to CG, no group difference reached significance.

Discussion

After a positive pilot-study (Ohnsorge 2000) this randomized controlled trial was designed to elucidate effects of a complex multimodal therapy in patients suffering from environmentally related diseases, with lasting chronic symptoms and proven toxic burden but below generally accepted toxic thresholds. All patients had serum levels of HCB, PCB and/or the sum of DDT and DDE above the 95th percentile of the upper reference level in biomonitoring studies but below regulatory limits. This usually is classified as a high exposure and allows the assumption that a causal relation may be present between symptoms and toxic body burden although serum concentrations were still below NOAEL values; therefore toxicological dose response relations as usually seen in intoxicated persons may not be generalizable. In these patients (with symptoms and higher exposure but still below toxicologically accepted NOAEL levels) an increased sensitivity is assumed as a contributing factor. Inclusion criteria like sensitivity to more than one chemical, lasting severe symptoms and exclusion of preexisting psychiatric illnesses were chosen to exclude patients with overt psychosomatic diseases.

The objective of this study was to test the efficacy of the complete treatment schedule; no evaluation of single elements is possible. The results indicated positive effects in subjective self ratings in both EG and CG. In addition, differences between the two treatment groups could be discovered, in particular in self rating scales.

The inclusion and exclusion criteria resulted in a limited number of patients. Among 170 patients initially contacted, only 50 fulfilled all inclusion criteria; the additional inclusion criteria "sensitivity to more than one chemical" and "lack of hypochondricity or psychotizism" further excluded another 13 patients. The remaining 36 study patients had less psychic symptoms than apparent in the general patient population with "toxic burden" in environmental ambulances.

In order to separate specific and nonspecific effects a waiting group was included to compare effects against a background development. It is assumed that comparison with the waiting group will uncover all therapeutic effects, whereas comparison with the control group would allow to discriminate between specific from nonspecific therapeutic effects, e.g. comparable intensity of patient doctor contact or infusion treatment. The only experimental variation between experimental and control treatment groups was the specificity of the treatment. Since this study was designed as a randomized controlled trial, comparison of the three groups can uncover effects dependent on treatment intensity and effects dependent on duration and contact time alone.

The greatest benefit was observed for EG compared to WG and CG. The results were highest for subjective variables, in particular in the complaint list (B-L). This questionnaire mainly assesses somatic complaints (e.g., nausea, back pain, short breath). Therefore, our results state positive effects of the experimental treatment predominately in aspects of somatic well-being. The difference between EG and WG is strong (d=1.41, cf. Cohen 1988) and includes specific and nonspecific therapy factors. The difference between EG and CG is intermediate (d=0.70) and pertains to specific treatment elements (physical exercises, hyperthermia, massage, lymph drainage, progressive muscle relaxation, vitamin and antioxidant supplementation). Our data also show that the effects lasted longer for EG patients (5 weeks after therapy) as compared to the CG.

No significant positive effects could be detected in neuropsychological tests. However, a tendency for improvement was seen in information processing, concentration ability and short term memory, with effect sizes of d = 0.37–0.68 standard deviations when comparing EG versus WG. Differences were more pronounced in time-restricted tests like ZVT, d2 and the restricted word reproduction test. These methods also test concentration ability.

Our data indicate a major health benefit for patients in the experimental group that arguably is no "placebo effect". Interestingly biomonitoring variables, i.e. serum concentrations of toxic compounds indicated a higher burden after therapy than before. A possible explanation is that mobilization and subsequent increase in serum concentrations of lipophilic compounds result in a lasting excretion. Our data are in agreement with this assumption. Studies investigating fatty tissue concentrations from biopsy samples indicate that significant reductions occur only after a couple of month. Due to time constraints and the necessary invasive procedure for fat biopsies these parameters were not included in this study.

Patients in the control therapy group as compared to the waiting group also received some benefit. This is probably due to the fact that these patients had 20 days of staying in the environmental unit (5–6 hours a day) and physician compassion. This may be considered as a treatment in itself. Therefore some positive effects had to be expected in this control group as compared to the waiting group.

Study limitation

Some limitations to our results may pertain to the short post treatment observation of five weeks, as well as the small patient number. Stringent inclusion criteria allow a homogenous study population but do not allow recruiting a large patient collective. Being able to identify and allocate effects to methodological parameters

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was tantamount resulting in small patient numbers. Changing the study design would have resulted in less homogenous patient groups and likely in decreased reliability by introducing uncontrolled parameters. Even our low patient number elucidated important differences between the experimental groups as well as in comparison to the waiting group. A lasting effect is seen five weeks after treatment termination indicating lasting health changes due to the selected multimodal treatment schedule.

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