Tailored Therapist-Guided Internet-Based Cognitive Behavioral Treatment for Psoriasis: A Randomized Controlled Trial

Sylvia van Beugen^{a, b} Maaïke Ferwerda^{a, b} Saskia Spillekom-van Koulil^{b, c}
Jurgen V. Smit^f Manon E.J. Zeeuwen-Franssen^e Elisabeth B.M. Kroft^g
Elke M.G.J. de Jong^c Marisol E. Otero^c A. Rogier T. Donders^d
Peter C.M. van de Kerkhof^c Henriët van Middendorp^{a, b} Andrea W.M. Evers^{a, b}

^aHealth, Medical and Neuropsychology Unit, Institute of Psychology, Leiden University, Leiden, Departments of
^bMedical Psychology, ^cDermatology and ^dHealth Evidence, Radboud university medical center, and ^eDepartment of
Dermatology, Canisius-Wilhelmina Hospital, Nijmegen, ^fDepartment of Dermatology, Rijnstate Hospital, Velp, and
^gDepartment of Dermatology, Ziekenhuisgroep Twente, Almelo, The Netherlands

Key Words

Cognitive-behavioral treatment · Tailored personalized treatment · Dermatology · Effectiveness · Impact of illness · Internet-based treatment · Intervention · Psoriasis · Psychodermatology · Randomized controlled trial · Working alliance

Abstract

Objective: Patients with somatic conditions, such as psoriasis, frequently suffer from high burden of their disease in daily life and might benefit from internet-based cognitive behavioral therapy (ICBT) tailored to their adjustment problems. The aim of this multicenter randomized controlled trial was to examine the effects of therapist-guided, individually tailored ICBT in a clinical sample of patients with psoriasis. **Methods:** A total of 131 patients with psoriasis, who were screened for a psychological risk profile, were randomized to either care as usual (CAU, $n = 66$) or ICBT in addition to CAU ($n = 65$). Participants filled out standardized self-report questionnaires assessing

physical and psychological functioning and impact on daily activities at baseline, posttreatment assessment, and 6-month follow-up. **Results:** In covariate-controlled linear mixed-model analyses, significantly larger improvements in ICBT compared to CAU were found in the primary outcomes physical functioning ($p = 0.03$, $d = 0.36$) and impact on daily activities ($p = 0.04$, $d = 0.35$), but not in psychological functioning ($p = 0.32$), up to 6 months after treatment compared to baseline. In explorative analyses, the working alliance measured at the beginning of ICBT treatment predicted improved physical ($p = 0.02$) and psychological ($p < 0.001$) outcomes. **Conclusions:** Results underline the promise of therapist-guided, individually tailored ICBT to improve physical functioning and reduce the impact of psoriasis on daily activities in patients with a psychological risk profile. Establishing a good therapeutic relationship early on may be an important factor that influences treatment outcomes in personalized ICBT interventions. Further research is needed to evaluate ICBT effectiveness in additional samples and to explore its underlying mechanisms.

© 2016 The Author(s)
Published by S. Karger AG, Basel

Introduction

Psoriasis is one of the most common immune-related chronic dermatological conditions [1] and is known for its high disease burden in daily life [2]. Patients frequently experience problems with mood, distress, and social impairments in addition to the burden of physical symptoms [3–6]. These problems may also negatively impact upon skin status, disease course, adherence, and dermatological treatment success [7–11]. Patients with a psychological profile of elevated levels of distress (an estimated 30–40%) are known to be at risk for long-term adjustment problems [3, 12] and might benefit from cognitive behavioral therapy (CBT), as it has shown to improve physical and psychological functioning in patients with chronic somatic conditions [13–16], including dermatological conditions [17–20]. Over the last decade, CBT has increasingly been offered online, which may facilitate intervention reach, increase cost-effectiveness and time-efficiency, and reduce possible barriers to following a psychological intervention [21, 22].

While systematic reviews show favorable effects of internet-based CBT (ICBT) for chronic somatic conditions [23–25], research in dermatological conditions is scarce. One randomized controlled trial (RCT) showed positive effects of unguided ICBT on anxiety and quality of life in patients with psoriasis but was limited by high dropout rates [26]. Therapist guidance may improve adherence [27, 28] and treatment effects [29–31], and patients tend to prefer guidance in ICBT [22, 32]. Furthermore, ICBT is usually based on standardized protocols [33], whereas recent findings underline the promise of less studied individually tailored interventions [34–36].

Despite the promising effects of therapist-guided, individually tailored ICBT in other conditions, its effects have not been examined in dermatological conditions. Possible predictors and correlates of treatment outcomes, including the therapeutic relationship [37, 38] and adherence [39], also remain unexplored in this group. Therefore, this study examined the effectiveness of therapist-guided, individually tailored ICBT for patients with psoriasis, expecting greater improvements in physical and psychological functioning and reduced impact on daily activities in ICBT compared to care as usual (CAU). In addition, sociodemographic, disease-related, and treatment-related predictors and correlates of treatment effects were explored.

Methods

Participants and Procedure

Study participants were recruited through outpatient dermatology departments of one academic and three non-academic hospitals and through the Dutch Psoriasis Association (fig. 1). Inclusion criteria were a diagnosis of psoriasis, age ≥ 18 years, and a positive psychological risk profile, i.e. Impact of chronic Skin Disease on Daily Life (ISDL) score of ≥ 5 for anxiety and/or ≥ 21 for negative mood [40, 41]. Exclusion criteria were psychological (i.e. diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) [42]) and/or physical comorbidity interfering with the study protocol, current psychological treatment, current photo(chemo)therapy, pregnancy, lack of access to a computer and/or internet, and illiteracy.

This study had an open-label parallel-group RCT design. An independent person randomized the participants (allocation ratio: 1:1) using a computerized program that minimized on age, gender, educational level, recruitment site, self-assessed disease severity, and medication use. The patients were randomized to either CAU (regular dermatological care) or ICBT in addition to CAU. A member of the research team informed the participants by phone and letter about treatment assignment. ICBT interventions took place between July 2010 and October 2014. Measurements were collected between June 2010 and April 2015. Study assessments were conducted at baseline, posttreatment assessment (CAU: 6 months after baseline), and 6-month follow-up (CAU: 12 months after baseline). The study was approved by the regional medical ethics committee, registered in the Dutch Trial Registry (NTR2436), and conducted in accordance with the Declaration of Helsinki [43]. All participants provided written informed consent.

ICBT Intervention

Patients randomized to the ICBT condition received an internet-based, therapist-guided CBT intervention aimed to reduce the impact of psoriasis on daily life, which was based on previous evidence-based face-to-face interventions [41, 44]. The intervention consisted of five flexible treatment modules containing a broad variety of cognitive and behavioral techniques focused on themes that patients often experience problems with: itch, pain, fatigue, negative mood, and social relationships. The participants started with two face-to-face intake sessions with their therapist (a psychologist), in which individual treatment goals were discussed. Next, patients received a telephone-based instruction of the intervention website by a researcher to ensure that they were capable of working with the program from home. The patients then started with the individually tailored ICBT intervention by logging on to the secure intervention website. Choice of treatment modules and individual assignments within these modules were determined based on individual patient goals, therapist's judgment, and screening procedures [see also 45]. The patients received personalized written feedback on their assignments from their therapist approximately once a week. Intervention duration and content varied between participants, depending on treatment goals, with a mean duration of 25 ± 12 weeks (range 1–57 weeks). For a more detailed description of ICBT modules, therapists, intervention use, and adherence, see online supplementary methods and results (see www.karger.com/doi/10.1159/000447267 for all online suppl. material).

Fig. 1. CONSORT flow diagram of participants. CWZ = Canisius-Wilhelmina Hospital, Nijmegen; PVN = Dutch Psoriasis Association; RS = Rijnstate Hospital, Velp; RUMC = Radboud university medical center, Nijmegen; ZGT = Ziekenhuis Groep Twente, Almelo.

Instruments

Primary and Secondary Outcomes. The primary outcome was the impact of psoriasis on daily life, measured on three domains, for which total scores were computed (composite scores: the overall average of normalized (z-)scores of the questionnaires included in each domain): (1) psychological functioning, consisting of negative mood (ISDL) [40], anxiety (ISDL) [40], and depressive symptoms (Beck Depression Inventory) [46, 47]; (2) physical functioning, consisting of itch (ISDL) [40] and fatigue (Checklist Individual Strength) [48]; and (3) impact on daily activities, consisting of role limitations due to physical health problems and role limitations due to emotional problems (RAND-36 Health Status Inventory) [49, 50]. Secondary outcomes consisted of clinician-rated (Psoriasis Area and Severity Index, PASI) [51] and self-reported disease severity (self-administered PASI) [52], and dermatological treatment compliance.

Predictors and Correlates of Treatment Outcome. Sociodemographic (age, sex, educational level, and marital status), disease-related (disease severity and duration), and treatment-related variables (working alliance between patient and ICBT therapist: Working Alliance Inventory – Short Form [53–55], ICBT adher-

ence, website logins) were examined as possible predictors and correlates of treatment outcomes. Further measurement details of all study variables can be found in the online supplementary methods and results.

Data Analysis

Baseline characteristics were compared with *t* tests and χ^2 tests. Primary analyses were conducted using linear mixed-effects modeling, which has superior qualities with regard to missing values [56] and makes use of all available data, making this a full intention-to-treat analysis. Models were fitted with full information maximum-likelihood estimation. Between-group effects at post-treatment assessment and follow-up were analyzed with baseline scores of dependent variables as covariates. Time was operationalized as a continuous variable, and posttreatment assessment varied across participants as a result of different intervention lengths. Fixed linear effects of time and condition were included as well as random effects of intercept. Primary analyses were conducted including all variables included in the randomization (age, sex, educational level, recruitment site, systemic medication use, etanercept use, and disease severity) as covariates [57]. In secondary anal-

Table 1. Baseline sociodemographic and disease-related characteristics of the ICBT and CAU groups

Characteristic	ICBT + CAU (n = 65)	CAU (n = 66)
Male gender	33 (50.8)	34 (51.5)
Age, years	52.69 ± 11.27 (24–73)	53.45 ± 13.81 (19–79)
Married/living together	46 (70.8)	53 (80.3)
Educational level		
Primary	1 (1.5)	4 (6.1)
Secondary	44 (67.7)	43 (65.2)
Tertiary	20 (30.8)	19 (28.8)
Disease severity (PASI) ¹	5.99 ± 5.61 (1–31) ³	4.20 ± 2.87 (0–13) ³
Disease severity (SAPASI) ¹	5.27 ± 3.29 (1–19) ³	4.48 ± 2.41 (0–12) ³
Disease duration, years	18.03 ± 13.76 (0–59) ³	15.16 ± 16.35 (0–65) ³
Systemic treatment ²	25 (44.6) ³	17 (29.3) ³

Data are presented as mean ± SD (range) or n (%), as appropriate. SAPASI = Self-administered PASI.

¹ Due to unequal distribution of Psoriasis Area and Severity Index (PASI) and SAPASI scores, transformed variables were used in analyses (see Methods); untransformed scores are displayed in this table.

² Number of patients reporting use of systemic treatment.

³ 2–12 missings.

yses, results were reported (1) without covariates (see Results) and (2) excluding ICBT dropouts/non-starters (see online suppl. methods and results).

Between-group Cohen's *d* type of effect sizes were calculated, dividing the difference in the estimated marginal means of the primary analyses of the two groups by their pooled pretreatment SD. Within-group Cohen's *d* effect sizes were calculated by dividing the difference in pre- and posttreatment assessment means by pre-assessment SDs. Effect sizes of 0.2, 0.5, and 0.8 were considered small, moderate, and large, respectively [58]. Unstandardized effect sizes were defined as raw mean differences between ICBT and CAU.

Pearson's correlation coefficients were calculated between change in primary outcomes (residual gain scores) and selected sociodemographic, disease-related, and treatment-related variables [60]. All analyses were conducted in IBM SPSS v21. A power analysis with 80% power indicated that a sample size of two groups of 65 patients was needed, assuming the effect size *d* = 0.50 (α = 0.05), based on previous ICBT studies for physical and psychological conditions [61]. Statistical significance was accepted at p < 0.05. In explorative analyses examining correlates of treatment effects, tendencies towards significant effects (p < 0.10) were not reported for stringency reasons.

Results

Between June 2010 and November 2013, 751 patients were screened, and 131 patients were randomized to either ICBT (*n* = 65) or CAU (*n* = 66). Means and SDs of selected sociodemographic and disease-related variables are presented in table 1, and baseline values on primary

outcomes and their subcomponents, as well as secondary outcomes, are presented in tables 2 and 3. These values did not differ between groups ($p \geq 0.10$), with the exception of a tendency towards higher levels of fatigue (p = 0.08) and higher clinician-rated disease severity (p = 0.03) in ICBT compared to CAU. Disease severity was generally mild to moderate, with 7.6% of patients having severe psoriasis (PASI >10) [62].

Attrition

A total of 73.3% of patients filled out posttreatment measurements, and 62.6% completed 6-month follow-up measurements (fig. 1). The ICBT intervention dropout rate was 26.2%: 10 patients did not start treatment (non-starters, 15.4%), 6 patients dropped out during treatment (non-completers, 9.2%), and 1 patient (1.5%) died during treatment as a result of comorbidity unrelated to the treatment. Reported reasons for ICBT dropout and differences between completers and dropouts can be found in the online supplementary methods and results.

ICBT Treatment Satisfaction

Patients in the ICBT group who filled out posttreatment evaluation questionnaires (*n* = 41) were satisfied with the ICBT intervention and gave the overall intervention a mean score of 7.64 ± 1.71 and user friendliness 7.72 ± 1.32 out of 10. A majority of 85.3% of patients would recommend the treatment to a friend or relative with a chronic somatic condition, and 87.7% of patients

Table 2. Means and SDs of each measurement point on primary outcome measures (total scores) and their subcomponents, including results of linear mixed-model analyses and accompanying effect sizes

Measurement	ICBT + CAU			CAU			Standard- ized effect size	Unstandardized effect size (95% CI)	Linear mixed models	
	mean	SD	n	mean	SD	n			effect	p value
<i>Psychological functioning</i>										
Total score (composite)										
Pre	0.02	0.87	60	−0.01	0.85	59	0.17	0.14 (−0.14 to 0.43)	Time Group	0.22
Post	−0.51	0.74	44	−0.29	0.92	49				
Follow-up	−0.49	0.90	37	−0.41	0.84	45				
Negative mood (ISDL) ¹										
Pre	5.29	3.77	60	5.39	3.72	58	0.06	0.06 (−0.28 to 0.40)	Time Group	0.35
Post	3.69	3.36	44	4.60	3.21	49				
Follow-up	3.86	3.65	37	4.11	3.53	45				
Anxiety (ISDL)										
Pre	21.85	4.61	60	22.10	4.58	60	0.24	1.09 (−0.57 to 2.74)	Time Group	0.28
Post	19.36	4.37	43	21.02	5.74	48				
Follow-up	19.45	5.38	37	20.27	5.03	45				
Depressive symptoms (BDI)										
Pre	12.78	7.50	60	11.50	6.23	58	0.15	1.01 (−1.28 to 3.30)	Time Group	0.24
Post	8.46	5.34	45	8.89	6.82	49				
Follow-up	8.53	6.72	37	8.69	6.36	45				
<i>Physical functioning</i>										
Total score (composite)										
Pre	0.11	0.73	60	−0.12	0.79	58	0.36	0.27 (0.02 to 0.52)	Time Group	0.13
Post	−0.55	0.75	43	−0.36	0.73	48				
Follow-up	−0.48	0.77	37	−0.55	0.68	42				
Fatigue (CIS-f)										
Pre	37.70	10.68	60	34.31	10.30	59	0.37	3.84 (0.09 to 7.59)	Time Group	0.09
Post	30.77	12.46	44	33.58	9.19	49				
Follow-up	31.19	11.65	37	31.40	10.09	44				
Itch (ISDL)										
Pre	9.44	3.50	60	9.06	3.75	59	0.17	0.61 (−0.56 to 1.77)	Time Group	0.44
Post	7.09	3.51	44	7.44	3.67	49				
Follow-up	7.44	3.32	37	6.88	2.97	43				
<i>Impact on daily activities</i>										
Total score (composite)										
Pre	0.03	0.71	58	−0.04	0.89	57	0.35	0.28 (0.01 to 0.55)	Time Group	0.12
Post	0.38	0.55	43	0.25	0.88	46				
Follow-up	0.37	0.69	37	0.34	0.79	43				
Emotional role functioning (RAND-36)										
Pre	78.16	35.07	58	67.54	39.89	57	0.33	12.12 (0.64 to 23.61)	Time Group	0.05
Post	86.36	23.09	44	76.09	38.27	46				
Follow-up	87.39	26.47	37	85.61	32.47	44				
Physical role functioning (RAND-36)										
Pre	53.02	41.90	58	58.89	43.09	60	0.32	13.34 (0.46 to 26.22)	Time Group	1.00
Post	72.09	36.68	43	73.94	40.03	47				
Follow-up	70.95	41.04	37	70.45	40.08	44				

All means and SDs are presented as uncorrected scores. BDI = Beck Depression Inventory; CIS-f = Checklist Individual Strength – fatigue; ISDL = Impact of Skin Disease on Daily Life; RAND-36 = RAND-36 Health Status Inventory.

¹ Due to unequal distribution of ISDL negative mood, transformed variables were used in analyses (see Methods); untransformed scores are displayed in this table.

Table 3. Means and SDs of each measurement point on secondary outcome measures, including results of linear mixed-model analyses and accompanying effect sizes

Measurement	ICBT + CAU			CAU			Standard- ized effect size	Unstandardized effect size (95% CI)	Linear mixed models	
	mean	SD	n	mean	SD	n			effect	p value
Clinician-assessed disease severity (PASI) ¹										
Pre	5.99	5.61	54	4.20	2.87	56				
Post	5.04	4.59	25	3.79	2.94	42			Time	0.34
Follow-up	4.76	3.47	22	3.40	2.63	37	0.02	0.01 (−0.32 to 0.35)	Group	0.94
Self-assessed disease severity (SAPASI) ¹										
Pre	5.27	3.29	59	4.48	2.41	54				
Post	4.61	5.39	44	3.95	2.26	43			Time	1.00
Follow-up	4.51	3.32	35	3.75	2.03	42	0.25	0.16 (−0.12 to 0.45)	Group	0.25
Dermatological treatment compliance										
Pre	3.96	1.11	59	4.09	1.03	58				
Post	4.02	1.21	41	4.02	0.98	44			Time	0.82
Follow-up	3.91	1.22	31	3.89	1.20	40	−0.11	−0.12 (−0.52 to 0.28)	Group	0.55

All means and SDs are presented as uncorrected scores. SAPASI = Self-administered PASI.

¹ Due to unequal distribution of Psoriasis Area and Severity Index (PASI) and SAPASI scores, transformed variables were used in analyses (see Methods); untransformed scores are displayed in this table.

believed the treatment would have long-term positive effects (somewhat/probably/certainly); 60% of patients indicated a preference for internet-based treatment over other forms of treatment (phone-based: 5.0%, face to face: 27.5%) for future treatment, and an additional 7.5% gave internet-based treatment a shared first place with one or more other modalities.

Primary Outcomes

Results on primary outcomes and their subcomponents, including effect sizes, are presented in table 2 and figure 2.

Psychological Functioning

In linear mixed-model analyses controlling for previously specified covariates, no significant differences were found between ICBT and CAU regarding psychological functioning at posttreatment assessment and 6-month follow-up ($p = 0.32$) or on its subcomponents negative mood, anxiety, and depressive symptoms (all $p \geq 0.20$). The lack of significant main effects of time ($p \geq 0.22$) indicated that these outcomes were stable across posttreatment assessment and 6-month follow-up. Similar results were obtained in secondary analysis including no other covariates than baseline values of the dependent variable ($p \geq 0.19$).

Physical Functioning

Significantly larger improvements in ICBT compared to CAU were found for physical functioning up to 6 months after treatment compared to baseline ($F_{1, 76.29} = 4.60$, $p = 0.03$, $d = 0.36$), with significant effects for fatigue ($F_{1, 74.53} = 4.16$, $p = 0.04$, $d = 0.37$) but not for itch ($p = 0.30$). These outcomes were stable across posttreatment assessment and 6-month follow-up, with the exception of fatigue, which tended to be lower at posttreatment assessment than at 6-month follow-up ($p = 0.09$). In secondary analysis including no other covariates than baseline values of the dependent variable, a tendency towards greater improvement in ICBT compared to CAU was found for fatigue ($p = 0.08$) and no significant between-group differences for itch or total physical functioning ($p \geq 0.16$).

Impact on Daily Activities

Significantly larger improvements in ICBT compared to CAU were found for impact on daily activities up to 6 months after treatment compared to baseline ($F_{1, 81.48} = 4.18$, $p = 0.04$, $d = 0.35$), with significant effects on both subcomponents: role limitations due to emotional problems ($F_{1, 132} = 4.36$, $p = 0.04$, $d = 0.33$) and role limitations due to physical health problems ($F_{1, 81.99} = 4.25$, $p = 0.04$, $d = 0.32$). The improvements in role limitations due to emotional problems at posttreatment assessment were further enlarged at follow-up ($p = 0.047$), while other out-

Fig. 2. Baseline, posttreatment assessment, and 6-month follow-up scores on primary outcome measures, i.e. total scores of psychological functioning (a), physical functioning (b), and impact on daily activities (c) for the ICBT and CAU groups, presented as means $\pm$ SEM. Negative scores indicate improved psychological and physical functioning in a and b, and positive scores indicate reduced impact on daily activities in c.

comes remained stable. In secondary analysis including no other covariates than baseline values of the dependent variable, no between-group differences were found ($p \geq 0.17$).

Disease Severity and Compliance

Results on self-reported and clinician-assessed disease severity and dermatological treatment compliance, in-

cluding effect sizes, are reported in table 3. No between-group differences were found for any of these outcomes, with or without covariates (all $p \geq 0.25$).

Within-Group Improvements

For primary outcome measures, ICBT within-group improvements were large for physical functioning ($d = 0.81$ – 0.90) and moderate for psychological functioning ($d = 0.59$ – 0.61) and impact on daily activities ($d = 0.48$ – 0.51). CAU within-group improvements were small to moderate for physical functioning ($d = 0.30$ – 0.56), psychological functioning ($d = 0.33$ – 0.47), and impact on daily activities ($d = 0.33$ – 0.43).

Predictors and Correlates of Treatment Effects

To explore which patients benefitted most from treatment, treatment-related variables (working alliance with the therapist, treatment duration, and ICBT adherence including patient ratings, therapist ratings, and website logins) were correlated with change in primary outcomes. Results indicated that a better working alliance with the therapist at the beginning of treatment was associated with greater pre- to posttreatment assessment improvements in psychological ($r = -0.66$, $p < 0.001$) and physical ($r = -0.42$, $p = 0.02$) functioning but not with change in impact on daily activities ($r = 0.18$, $p = 0.34$). No significant associations of change in primary outcomes with treatment duration, ICBT adherence were found, nor with the sociodemographic and disease-related variables age, sex, educational level, disease duration, and disease severity (all $p \geq 0.17$).

Discussion

This first trial on the effectiveness of individually tailored, therapist-guided ICBT for patients with psoriasis who had a psychological risk profile indicated that ICBT as an adjunct to CAU had more beneficial effects on physical functioning and the impact of psoriasis on daily activities compared to CAU alone. When analyzing who benefits most from ICBT, the working alliance between patient and therapist measured at the beginning of treatment was related to improved physical and psychological outcomes, suggesting that the establishment of a good patient-therapist relationship early on is of considerable importance in guided ICBT.

Results on primary outcomes showed significantly larger improvements in ICBT compared to CAU on physical functioning and impact on daily activities. Ef-

fects on physical functioning were driven by improvements in fatigue, which is a frequent and disabling symptom in many chronic inflammatory conditions [63]. Patients often characterize fatigue as one of the most burdensome aspects of their condition [63], which was also reflected in the current trial; mean baseline scores were above the cutoff point for extreme fatigue [48], while means on other outcomes were comparable to norm groups of healthy individuals. In addition, the fatigue module was frequently chosen as the preferred treatment module in this trial. ICBT patients also improved more on impact on daily activities, indicating that patients who received ICBT felt significantly less limited by their physical health and emotional problems in performing their work or daily activities than patients who received CAU.

In contrast, no significant between-group effects were observed for psychological functioning. This is surprising, considering that patients were screened for elevated levels of distress and that negative mood was a frequently applied treatment module. Despite screening, baseline psychological functioning scores were generally comparable to healthy populations, as many patients scored just above cutoff values, and 22% of the sample that scored above cutoff values at screening did not fulfill these criteria anymore at baseline. As meta-analyses suggest that patients with higher distress scores demonstrate larger CBT effects [64, 65], distress levels may have been too low for patients to benefit sufficiently from ICBT. Low baseline scores were also cited as a reason for the small effects found in a recent meta-analysis on (I)CBT for long-term conditions, i.e. effect sizes of 0.20–0.21 for anxiety and depression [66], comparable to an earlier meta-analysis [24].

Moderate to large ICBT effects were found for primary outcomes and their subcomponents, which were comparable to similar tailored face-to-face CBT interventions [41, 67]. However, between-group effect sizes were small, which was explained by larger than expected CAU effects. This may also explain why significant effects for physical functioning were found for fatigue but not for itch: post-treatment ICBT effect sizes were similar for itch and fatigue, while CAU effects were moderate for itch and small to non-existent for fatigue. As high standards of care are generally associated with greater CAU effects on physical and psychological outcomes [68], the fact that 42% of patients were recruited from a university medical center might have played a role in these findings. The timing of participant recruitment may have also contributed; patients were often recruited when starting dermatological treatment and many patients reported changes in system-

ic medication during the trial. In future research, differential screening procedures may decrease these confounding effects and possibly optimize treatment effects by screening patients who experience elevated distress levels despite being on a stable dermatological regimen, for example.

A better therapeutic relationship (working alliance) measured early in treatment showed moderate to large correlations with improvements in physical and psychological outcomes, supporting the relevance of the therapeutic relationship in ICBT. These findings are in line with evidence in face-to-face CBT [69–71] and expand upon scarce evidence from studies on internet-based interventions [38, 72–75]. Associations of early working alliance scores with treatment outcome were somewhat higher than those observed in previous studies, possibly because the therapeutic relationship is of greater importance in highly personalized interventions. Treatment outcomes were not associated with the number of logins or treatment length, partially corresponding with previous conflicting evidence [39, 76, 77]. While logins and treatment length have advantages in being objective measures, they may not adequately reflect interaction with treatment content and user experiences.

The characteristics of this study differed in some important ways from many previously conducted ICBT studies. ICBT was compared to CAU in a clinical sample, including a 6-month follow-up, while most ICBT studies have typically included community-based and self-referred samples, waiting-list comparisons, and posttreatment data only [for summary, see 24]. While significant effects were found in this trial, the effects were typically small and were not all found in secondary analyses that did not include prespecified covariates. Consistent with our findings, recent meta-analytic evidence shows that the effects of ICBT are typically smaller in studies with a CAU than a waiting-list comparison and in clinical samples than in community-based samples, and the effects are often non-significant on the rare occasion that long-term follow-up results are meta-analyzed [78–80]. This underlines the need for further in-depth research regarding the influence of methodological, sample, and intervention characteristics on trial results.

Both the limitations and strengths of the present study have to be considered. Firstly, similar to previous studies [for summary, see 24], a substantial proportion of patients did not complete ICBT and/or failed to return questionnaires. In line with previous evidence, attrition rates were higher in ICBT than in CAU [81]. While drop-out rates were somewhat lower than in a study of non-

tailored ICBT for psoriasis [26], the fact that they were generally comparable to previous studies does not support the often-cited idea that tailored interventions are associated with lower dropout rates. However, the majority of dropouts were non-starters and therefore not exposed to treatment content. Furthermore, the relatively long ICBT duration, i.e. a mean duration of 25 weeks compared to 8 weeks in many other interventions [24], may have increased dropout rates, which often increase progressively with intervention duration [82]. Lower baseline disease severity was associated with higher ICBT dropout, possibly because these patients experienced a lower disease burden and were therefore less motivated to adhere to a program aimed to decrease the impact of psoriasis on daily life. The main strengths of the current study include the application of a unique individually tailored and therapist-guided intervention in a target population that is generally underserved when it comes to psychological support. Methodological strengths include the multicenter RCT design comparing ICBT to CAU in a clinical sample, including a 6-month follow-up.

To conclude, individually tailored, therapist-guided ICBT led to significantly greater improvements compared to CAU for physical functioning and impact on daily activities in a clinical sample of patients with a psychological risk profile. The therapeutic relationship showed moderate to large associations with better treatment effects, illustrating the importance of this relationship in guided ICBT. The results of this trial underline the promise of ICBT for dermatological conditions in a clinical setting, which is supported by previous studies in other conditions showing that ICBT interventions can be transferred to clinical practice with sustained effects and moderate to large effect sizes [83]. Future research

should focus on the working mechanisms and provide further evidence on how well these interventions translate into clinical practice. Furthermore, future research in additional samples (e.g. higher levels of distress and disease severity) should extend these findings to be able to draw robust conclusions on the effectiveness of individually tailored, therapist-guided psychological interventions for dermatological conditions.

Acknowledgments

This study was supported by grants from Pfizer (WS682746) and ZonMw (170992803). Pfizer and ZonMw were not involved in the study design, data collection, data analysis, manuscript preparation, or publication decisions. The authors of this manuscript are not aware of any conflict of interest influencing this work. Prof. Dr. Andrea Evers received research grants from ERC (European Research Council), NWO (The Netherlands Organization for Scientific Research), ZonMw, Pfizer, and the Nierstichting (Dutch Kidney Foundation). Henriët van Middendorp, Sylvia van Beugen, and Maaike Ferwerda are part of the research group conducting research funded by these grants. The authors are grateful to Nina Koch and Milou Looijmans for their help in collecting the data, to Saskia Spillekom-van Koulil, Tamara Bremer, Els Garritsen, Irene Vermeulen, Lieke Wirken, and Alicia Wijnakker for their work as online therapists, and to Marisol Otero, Jessica Terwindt-Slob, and Lisa Jacobs for conducting PASI assessments. The authors would also like to thank IPPZ for collaboration in the design of the online program and for ongoing technical support. Lastly, the authors would like to thank their patient research partners who contributed significantly throughout the development and study of the ICBT intervention: Henk van Duijn, Mariëtte Tomas-Krabbe, Ilse van Ee, and Hen Ros (deceased).

Disclosure Statement

The authors have no conflicts of interest to declare.

References

- Schon MP, Boehncke WH: Psoriasis. *N Engl J Med* 2005;352:1899–1912.
- Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ, Marks R, Naldi L, Weinstock MA, Wulf SK, Michaud C, Murray CJL, Naghavi M: The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol* 2014;134:1527–1534.
- Evers AW, Lu Y, Duller P, van der Valk PG, Kraaijmaat FW, van de Kerkhof PC: Common burden of chronic skin diseases? Contributors to psychological distress in adults with psoriasis and atopic dermatitis. *Br J Dermatol* 2005;152:1275–1281.
- Fortune DG, Richards HL, Griffiths CE: Psychologic factors in psoriasis: consequences, mechanisms, and interventions. *Dermatol Clin* 2005;23:681–694.
- Verhoeven EW, Kraaijmaat FW, van de Kerkhof PC, van Weel C, Duller P, van der Valk PG, van den Hoogen HJ, Bor JH, Schers HJ, Evers AW: Prevalence of physical symptoms of itch, pain and fatigue in patients with skin diseases in general practice. *Br J Dermatol* 2007;156:1346–1349.
- Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GB, Misery L, Szabo C, Linder D, Sampogna F, Evers AW, Halvorsen JA, Balieva F, Szepietowski J, Romanov D, Marron SE, Altunay IK, Finlay AY, Salek SS, Kupfer J: The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol* 2015;135:984–991.
- Evers AW, Verhoeven EW, Kraaijmaat FW, de Jong EM, de Brouwer SJ, Schalkwijk J, Sweep FC, van de Kerkhof PC: How stress gets under the skin: cortisol and stress reactivity in psoriasis. *Br J Dermatol* 2010;163:986–991.

- 8 Fortune DG, Richards HL, Kirby B, McElhone K, Markham T, Rogers S, Main CJ, Griffiths CE: Psychological distress impairs clearance of psoriasis in patients treated with photochemotherapy. *Arch Dermatol* 2003; 139:752–756.
- 9 Heller MM, Lee ES, Koo J: Stress as an influencing factor in psoriasis. *Skin Therapy Lett* 2011;16:1–4.
- 10 Tan X, Feldman SR, Chang J, Balkrishnan R: Topical drug delivery systems in dermatology: a review of patient adherence issues. *Expert Opin Drug Deliv* 2012;9:1263–1271.
- 11 Thorneoloe RJ, Bundy C, Griffiths CE, Ashcroft DM, Cordingley L: Adherence to medication in patients with psoriasis: a systematic literature review. *Br J Dermatol* 2013;168:20–31.
- 12 Gupta MA, Gupta AK: Psychiatric and psychological co-morbidity in patients with dermatologic disorders. *Am J Clin Dermatol* 2003;4:833–842.
- 13 Farrand P, Woodford J: Effectiveness of cognitive behavioural self-help for the treatment of depression and anxiety in people with long-term physical health conditions: a systematic review and meta-analysis of randomised controlled trials. *Ann Behav Med* 2015;49:579–593.
- 14 Matcham F, Rayner L, Hutton J, Monk A, Steel C, Hotopf M: Self-help interventions for symptoms of depression, anxiety and psychological distress in patients with physical illnesses: a systematic review and meta-analysis. *Clin Psychol Rev* 2014;34:141–157.
- 15 Morley S, Eccleston C, Williams A: Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain* 1999;80:1–13.
- 16 Price JR, Mitchell E, Tidy E, Hunot V: Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev* 2008;3:CD001027.
- 17 Fordham B, Griffiths CE, Bundy C: Can stress reduction interventions improve psoriasis? A review. *Psychology Health Med* 2013;18:501–514.
- 18 Fortune D, Richards H, Kirby B, Bowcock S, Main C, Griffiths C: A cognitive-behavioural symptom management programme as an adjunct in psoriasis therapy. *Br J Dermatol* 2002; 146:458–465.
- 19 Fortune DG, Richards HL, Griffiths CE, Main CJ: Targeting cognitive-behaviour therapy to patients' implicit model of psoriasis: results from a patient preference controlled trial. *Br J Clin Psychol* 2004;43:65–82.
- 20 Lavda A, Webb T, Thompson A: A meta-analysis of the effectiveness of psychological interventions for adults with skin conditions. *Br J Dermatol* 2012;167:970–979.
- 21 Ferwerda M, van Beugen S, van Burik A, van Middendorp H, de Jong EM, van de Kerkhof PC, van Riel PL, Evers AW: What patients think about E-health: patients' perspective on internet-based cognitive behavioral treatment for patients with rheumatoid arthritis and psoriasis. *Clin Rheumatol* 2013;32:869–873.
- 22 Hedman E, Ljótsson B, Lindefors N: Cognitive behavior therapy via the internet: a systematic review of applications, clinical efficacy and cost-effectiveness. *Expert Rev Pharmacoecon Outcomes Res* 2012;12:745–764.
- 23 Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E: Guided internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. *World Psychiatry* 2014;13:288–295.
- 24 van Beugen S, Ferwerda M, Hoeve D, Rovers MM, Spillekom-van Koulik S, van Middendorp H, Evers AW: Internet-based cognitive behavioral therapy for patients with chronic somatic conditions: a meta-analytic review. *J Med Internet Res* 2014;16:e88.
- 25 McCombie A, Gearry R, Andrews J, Mikocka-Walus A, Mulder R: Computerised cognitive behavioural therapy for psychological distress in patients with physical illnesses: a systematic review. *J Clin Psychol Med S* 2015;22:20–44.
- 26 Bundy C, Pinder B, Bucci S, Reeves D, Griffiths CE, Tarrier N: A novel, web-based, psychological intervention for people with psoriasis: the electronic Targeted Intervention for Psoriasis (eTIPS) study. *Br J Dermatol* 2013;169:329–336.
- 27 Andersson G: The promise and pitfalls of the internet for cognitive behavioral therapy. *BMC Med* 2010;8:82.
- 28 Titov N, Dear BF, Johnston L, Lorian C, Zou J, Wootton B, Spence J, McEvoy PM, Rapee RM: Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: randomised controlled trial. *PLoS One* 2013;8:e62873.
- 29 Johansson R, Andersson G: Internet-based psychological treatments for depression. *Expert Rev Neurother* 2012;12:861–869.
- 30 Newman MG, Szkodny LE, Llera SJ, Przeworski A: A review of technology-assisted self-help and minimal contact therapies for anxiety and depression: is human contact necessary for therapeutic efficacy? *Clin Psychol Rev* 2011;31:89–103.
- 31 Spek V, Cuijpers P, Nyklicek I, Riper H, Keyzer J, Pop V: Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. *Psychol Med* 2007; 37:319–328.
- 32 Berle D, Starcevic V, Milicevic D, Hannan A, Dale E, Brakoulias V, Viswasam K: Do patients prefer face-to-face or internet-based therapy? *Psychother Psychosom* 2015;84:61–62.
- 33 Andersson G, Cuijpers P: Pros and cons of online cognitive-behavioural therapy. *Br J Psychiatry* 2008;193:270–271.
- 34 Johansson R, Sjöberg E, Sjögren M, Johnsson E, Carlbring P, Andersson T, Rousseau A, Andersson G: Tailored versus Standardized internet-based cognitive behavior therapy for depression and comorbid symptoms: a randomized controlled trial. *PLoS One* 2012;7: e36905.
- 35 Carlbring P, Maurin L, Törngren C, Linna E, Eriksson T, Sparthar E, Strååt M, von Hage CM, Bergman-Nordgren L, Andersson G: Individually tailored, internet-based treatment for anxiety disorders: a randomized controlled trial. *Behav Res Ther* 2011;49:18–24.
- 36 Nordgren LB, Hedman E, Etienne J, Bodin J, Kadowaki Å, Eriksson S, Lindkvist E, Andersson G, Carlbring P: Effectiveness and cost-effectiveness of individually tailored internet-delivered cognitive behavior therapy for anxiety disorders in a primary care population: a randomized controlled trial. *Behav Res Ther* 2014;59:1–11.
- 37 Ferwerda M, van Beugen S, van Riel PC, van de Kerkhof PC, de Jong EM, Smit JV, Zeeuwen-Franssen ME, Kroft EB, Visser H, Vonkeman HE, Creemers MC, van Middendorp H, Evers AW: Measuring the therapeutic relationship in internet-based interventions. *Psychother Psychosom* 2015;85:47–49.
- 38 Sucala M, Schnur JB, Constantino MJ, Miller SJ, Brackman EH, Montgomery GH: The therapeutic relationship in e-therapy for mental health: a systematic review. *J Med Internet Res* 2012;14:e110.
- 39 Donkin L, Christensen H, Naismith SL, Neal B, Hickie IB, Glozier N: A systematic review of the impact of adherence on the effectiveness of e-therapies. *J Med Internet Res* 2011; 13.
- 40 Evers AW, Duller P, van de Kerkhof PC, van der Valk PG, de Jong EM, Gerritsen MJ, Otero E, Verhoeven EW, Verhaak CM, Kraaijaat FW: The Impact of Chronic Skin Disease on Daily Life (ISDL): a generic and dermatology-specific health instrument. *Br J Dermatol* 2008;158:101–108.
- 41 Evers AW, Kraaijaat FW, van Riel PL, de Jong AJ: Tailored cognitive-behavioral therapy in early rheumatoid arthritis for patients at risk: a randomized controlled trial. *Pain* 2002; 100:141–153.
- 42 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4, text rev. Washington, American Psychiatric Association, 2000.
- 43 World Medical Association: World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191.
- 44 Evers AW, Duller P, de Jong EM, Otero ME, Verhaak CM, van der Valk PG, van de Kerkhof PC, Kraaijaat FW: Effectiveness of a multidisciplinary itch-coping training programme in adults with atopic dermatitis. *Acta Derm Venereol* 2009;89:57–63.
- 45 Evers AW, Gieler U, Hasenbring MI, Van Middendorp H: Incorporating biopsychosocial characteristics into personalized healthcare: a clinical approach. *Psychother Psychosom* 2014;83:148–157.

- 46 Beck AT, Steer RA, Brown GK: Beck Depression Inventory-II. San Antonio, The Psychological Corporation, 1996.
- 47 Beck AT, Steer RA, Carbin MG: Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. *Clin Psychol Rev* 1988;8:77–100.
- 48 Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G: Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;38:383–392.
- 49 Hays RD, Morales LS: The RAND-36 measure of health-related quality of life. *Ann Med* 2001;33:350–357.
- 50 Van der Zee KI, Sanderman R, Heyink JW, de Haes H: Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. *Int J Behav Med* 1996;3:104–122.
- 51 Fredriksson T, Pettersson U: Severe psoriasis – oral therapy with a new retinoid. *Dermatologica* 1978;157:238–244.
- 52 Feldman SR, Fleischer AB Jr, Reboussin DM, Rapp SR, Exum ML, Clark AR, Nurre L: The self-administered Psoriasis Area and Severity Index is valid and reliable. *J Invest Dermatol* 1996;106:183–186.
- 53 Busseri MA, Tyler JD: Interchangeability of the Working Alliance Inventory and Working Alliance Inventory, Short Form. *Psychol Assess* 2003;15:193–197.
- 54 Horvath AO, Greenberg LS: Development and validation of the Working Alliance Inventory. *J Couns Psychol* 1989;36:223–233.
- 55 Bordin ES: The generalizability of the psychoanalytic concept of the working alliance. *Psychotherapy* 1979;16:252–260.
- 56 Gueorguieva R, Krystal JH: Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Arch Gen Psychiatry* 2004;61:310–317.
- 57 Tu D, Shalay K, Pater J: Adjustment of treatment effect for covariates in clinical trials: statistical and regulatory issues. *Drug Inf J* 2000;34:511–523.
- 58 Cohen J: Statistical Power Analysis for the Behavioral Sciences, ed 2. Hillsdale, Lawrence Erlbaum, 1988.
- 59 Rivest L-P: Statistical properties of Winsorized means for skewed distributions. *Biometrika* 1994;81:373–383.
- 60 Steketee G, Chambless DL: Methodological issues in prediction of treatment outcome. *Clin Psychol Rev* 1992;12:387–400.
- 61 Cuijpers P, van Straten A, Andersson G: Internet-administered cognitive behavior therapy for health problems: a systematic review. *J Behav Med* 2008;31:169–177.
- 62 Finlay AY: Current severe psoriasis and the rule of tens. *Br J Dermatol* 2005;152:861–867.
- 63 Skoie I, Ternowitz T, Jonsson G, Norheim K, Omdal R: Fatigue in psoriasis: a phenomenon to be explored. *Br J Dermatol* 2015;172:1196–1203.
- 64 Bower P, Kontopantelis E, Sutton A, Kendrick T, Richards DA, Gilbody S, Knowles S, Cuijpers P, Andersson G, Christensen H: Influence of initial severity of depression on effectiveness of low intensity interventions: meta-analysis of individual patient data. *BMJ* 2013;346:f540.
- 65 Driessen E, Cuijpers P, Hollon SD, Dekker JJ: Does pretreatment severity moderate the efficacy of psychological treatment of adult outpatient depression? A meta-analysis. *J Consult Clin Psychol* 2010;78:668–680.
- 66 Farrand P, Woodford J: Effectiveness of cognitive behavioural self-help for the treatment of depression and anxiety in people with long-term physical health conditions: a systematic review and meta-analysis of randomised controlled trials. *Ann Behav Med* 2015;1–15.
- 67 van Koulil S, van Lankveld W, Kraaimaat FW, van Helmond T, Vedder A, van Hoorn H, Donders R, de Jong AJ, Haverman JF, Korff KJ, van Riel PL, Cats HA, Evers AW: Tailored cognitive-behavioral therapy and exercise training for high-risk patients with fibromyalgia. *Arthritis Care Res (Hoboken)* 2010;62:1377–1385.
- 68 Ayling K, Brierley S, Johnson B, Heller S, Eiser C: How standard is standard care? Exploring control group outcomes in behaviour change interventions for young people with type 1 diabetes. *Psychol Health* 2015;30:85–103.
- 69 Horvath AO, Symonds BD: Relation between working alliance and outcome in psychotherapy: a meta-analysis. *J Couns Psychol* 1991;38:139–149.
- 70 Martin DJ, Garske JP, Davis MK: Relation of the therapeutic alliance with outcome and other variables: a meta-analytic review. *J Consult Clin Psychol* 2000;68:438–450.
- 71 van Andel P, Erdman RA, Karsdorp PA, Appels A, Trijsburg RW: Group cohesion and working alliance: prediction of treatment outcome in cardiac patients receiving cognitive behavioral group psychotherapy. *Psychother Psychosom* 2003;72:141–149.
- 72 Andersson G, Paxling B, Wiwe M, Vernmark K, Felix CB, Lundborg L, Furmark T, Cuijpers P, Carlbring P: Therapeutic alliance in guided internet-delivered cognitive behavioural treatment of depression, generalized anxiety disorder and social anxiety disorder. *Behav Res Ther* 2012;50:544–550.
- 73 Jasper K, Weise C, Conrad I, Andersson G, Hiller W, Kleinstäuber M: The working alliance in a randomized controlled trial comparing internet-based self-help and face-to-face cognitive behavior therapy for chronic tinnitus. *Internet Interv* 2014;1:49–57.
- 74 Nordgren LB, Carlbring P, Linna E, Andersson G: Role of the working alliance on treatment outcome in tailored internet-based cognitive behavioural therapy for anxiety disorders: randomized controlled pilot trial. *JMIR Res Protoc* 2013;2:e4.
- 75 White M, Stinson JN, Lingley-Pottie P, McGrath PJ, Gill N, Vijenthira A: Exploring therapeutic alliance with an internet-based self-management program with brief telephone support for youth with arthritis: a pilot study. *Telemed J E Health* 2012;18:271–276.
- 76 Christensen H, Griffiths K, Mackinnon A, Brittliffe K: Online randomized controlled trial of brief and full cognitive behaviour therapy for depression. *Psychol Med* 2006;36:1737–1746.
- 77 Shapiro DA, Barkham M, Rees A, Hardy GE, Reynolds S, Startup M: Effects of treatment duration and severity of depression on the effectiveness of cognitive-behavioral and psychodynamic-interpersonal psychotherapy. *J Consult Clin Psychol* 1994;62:522–534.
- 78 Farrand P, Woodford J: Impact of support on the effectiveness of written cognitive behavioural self-help: a systematic review and meta-analysis of randomised controlled trials. *Clin Psychol Rev* 2013;33:182–195.
- 79 Gellatly J, Bower P, Hennessy S, Richards D, Gilbody S, Lovell K: What makes self-help interventions effective in the management of depressive symptoms? Meta-analysis and meta-regression. *Psychol Med* 2007;37:1217–1228.
- 80 So M, Yamaguchi S, Hashimoto S, Sado M, Furukawa TA, McCrone P: Is computerised CBT really helpful for adult depression? A meta-analytic re-evaluation of CCBT for adult depression in terms of clinical implementation and methodological validity. *BMC Psychiatry* 2013;13:113.
- 81 Crutzen R, Viechtbauer W, Spigt M, Kotz D: Differential attrition in health behaviour change trials: a systematic review and meta-analysis. *Psychol Health* 2015;30:122–134.
- 82 Christensen H, Griffiths KM, Farrer L: Adherence in internet interventions for anxiety and depression: systematic review. *J Med Internet Res* 2009;11:e13.
- 83 Andersson G, Hedman E: Effectiveness of guided internet-based cognitive behavior therapy in regular clinical Settings. *Verhaltenstherapie* 2013;23:140–148.