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Boeschoten, R.E.; Dekker, J; Uitdehaag, B.M.J.; Beekman, A.T.F.; Hoogendoorn, A.W.; Collette, E.H.; Cuijpers, Pim; Nieuwenhuis, M.M.; van Oppen, P.

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Original Research Paper

Internet-based treatment for depression in multiple sclerosis: A randomized controlled trial

Rosa E Boeschoten, Joost Dekker, Bernard MJ Uitdehaag, Aartjan TF Beekman, Adriaan W Hoogendoorn, Emma H Collette, Pim Cuijpers, Magdalena M Nieuwenhuis and Patricia van Oppen

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Abstract

Background: Depression in multiple sclerosis (MS) patients is common but may stay untreated. Physical limitations impede face-to-face treatment. Internet-based treatment is therefore a promising tool for treating depression in MS.

Objectives: To investigate effectiveness of a guided Internet-based problem-solving treatment (IPST) for depressed MS patients.

Methods: MS patients with moderate or severe depressive symptoms were randomly assigned to IPST or a wait list control. Primary outcome was the change in depressive symptoms defined by a change in sum score on the Beck Depression Inventory Second Edition (BDI-II). Assessments took place at baseline (T0), within a week after the intervention (T1), and at 4 months follow-up (T2). Analyses were based on the intention-to-treat principle.

Results: A total of 171 patients were randomized to IPST ($n=85$) or a wait list control ($n=86$). T1 was completed by 152 (89%) and T2 by 131 patients (77%). The IPST group and wait list control showed large significant improvements in depressive symptoms, but no differences were found between groups at T1 ($d=0.23$; 95% confidence interval (CI)=(−4.03, 1.08); $p=0.259$) and T2 ($d=0.01$; 95% CI=(−2.80, 2.98); $p=0.953$).

Conclusion: We found no indication that IPST for MS patients with moderate or severe depression is effective in reducing depressive symptoms compared to a waiting list. Large improvements in the wait list control were unexpected and are discussed.

Keywords: Depression, multiple sclerosis, Internet-based treatment, problem-solving treatment, clinical trial

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Correspondence to:
RE Boeschoten
Department of Psychiatry, VU University Medical Center/GGZinGeest, A.J. Ernststraat 1187, 1081 HL Amsterdam, The Netherlands
r.boeschoten@ggzingeest.nl

Rosa E Boeschoten
Aartjan TF Beekman
Adriaan W Hoogendoorn
Magdalena M Nieuwenhuis
Patricia van Oppen
EMGO+ Institute for Mental Health and Care Research/ Department of Psychiatry, VU University Medical Center/GGZinGeest, Amsterdam, The Netherlands

Joost Dekker
Department of Psychiatry, VU University Medical Center/GGZinGeest, Amsterdam, The Netherlands/EMGO+ Institute for Mental Health and Care Research, VU University, Amsterdam, The Netherlands; Department of Rehabilitation Medicine, VU University Medical Center Amsterdam, The Netherlands

Bernard MJ Uitdehaag
Department of Neurology, Multiple Sclerosis Center, VU University Medical Center, Amsterdam, The Netherlands

Emma H Collette
Department of Medical Psychology, VU University Medical Center, Amsterdam, The Netherlands

Pim Cuijpers
EMGO+ Institute for Mental Health and Care Research, VU University, Amsterdam, The Netherlands/Department of Clinical, Neuro & Developmental Psychology, VU University, Amsterdam, The Netherlands

Introduction

Depression in multiple sclerosis (MS) is common (24%)[1] and has a large impact on quality of life. It is related to fatigue, cognitive dysfunction, working problems and disrupted social support and family systems and may adversely affect health outcome.[2,3] Cognitive behavioral therapy (CBT) is an effective treatment for depressed patients with medical conditions including MS.[4,5] Still, many MS patients remain untreated.[3] Under-treatment may be due to disease-related barriers such as transportation difficulties, physical immobility, fatigue and MS exacerbations that impede face-to-face treatment.[6]

Guided Internet-based cognitive behavioral therapy (ICBT) is considered a good alternative for face-to-face treatment.[7,8] ICBT is easily available, cost-effective, and can reach a large number of people with functional impairments due to physical health problems. Internet-based interventions demonstrated psychosocial benefits in chronic illness settings,[9] and research of telemedicine technologies in treating

depression in (housebound) MS patients was recently advised in MS guidelines.[3] Although this patient group may likely benefit from ICBT, there are still few publications on ICBT for depressed MS patients,[10–12] and the results are encouraging. In an uncontrolled pilot study, we found that Internet-based problem-solving treatment (IPST), CBT with a focus on developing sufficient coping skills, is a feasible treatment for depression in MS and may reduce depressive symptoms.[10]

Here, we present a randomized controlled trial (RCT) to investigate the effectiveness of guided IPST for depression in MS.[13] We aimed to examine effectiveness of IPST on the primary outcome measure depressive symptoms and on secondary outcome measures related to depression in MS such as anxiety, quality of life, fatigue, cognitive, and physical functioning.

Patients and methods

Trial design

A two-armed RCT in which an Internet-based guided self-help problem-solving treatment (IPST) was compared with a wait list control. An extensive description of the study protocol can be found elsewhere.[13] The trial was approved by the Medical Ethics Committee of the VU University Medical Center and registered with the Dutch Trial Registry (NTR2772).

Patients

MS patients were recruited at several MS centers throughout the Netherlands, and through calls in MS newsletters and Internet sites, and were invited to complete an online screening assessment. Patients (18 years or older) with sufficient command of Dutch language and Internet access were eligible to participate if they had (a) a diagnosis of MS (>3 months) and (b) a score of 20 or more on the Beck Depression Inventory Second Edition (BDI-II), indicating moderate or severe depression. Patients taking prescribed psychotropic medication for more than 6 weeks with stable dosage were allowed to participate. Those receiving psychotherapy or with an elevated risk for suicide assessed with item 9 of the BDI-II and an additional telephone interview were excluded. All patients gave written informed consent.

IPST

The guided self-help intervention "Minder Zorgen" ("Worry Less") was an existing and tested IPST that was adjusted for MS patients.[13] The intervention consisted of five sequential modules with text, examples and assignments that patients could access from their personal computers via the Internet. Patients were advised to complete one module per week but could extend the intervention period up to 10 weeks if extra time was needed. Support during the intervention was provided by trained psychologists and supervised psychology master students and consisted of weekly emails. Patients could contact their coach at any moment for additional support via the website. Support was directed to help the patient work through the intervention.

Patients randomized to the wait list control received no IPST. After completion of the 4 months follow-up assessment, they were offered the possibility to participate in the intervention.

Outcomes

Eligible and consenting patients were assessed at baseline (T0), within a week after the intervention (5–10 weeks) (T1), and at 4 months follow-up (T2). The wait list control was measured at the same moments in time. Data were collected by self-report measures administered through the Internet and a telephone interview at baseline by trained research staff.

The primary outcome was the change in depressive symptoms defined by a change in sum score on the BDI-II. Post hoc analyses for BDI-II subscale scores[14] and for moderate (BDI-II = 20–28) and severely (BDI-II $\geqslant$ 29) depressed patients at baseline were additionally performed (supplementary material). Secondary outcome measures were the anxiety subscales of the Hospital Anxiety and Depression Scale, Beck Anxiety Inventory, Fatigue Severity Scale, Multiple Sclerosis Neuropsychological Questionnaire, Multiple Sclerosis Impact Scale, EuroQol quality of life measure, subscales of the Social Problem Solving Inventory-Revised, and the abbreviated version of the Pearlin Mastery Scale.

At baseline, a clinical diagnosis of a Depression Disorder and/or Anxiety Disorder according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision; DSM-IV-TR) criteria was established by a standard telephone interview using the Composite International Diagnostic Interview. The telephone version of the Expanded Disability Status Scale was used to assess physical (MS) functioning and disability level. Other additional baseline measures concerned sociodemographic and MS-specific questions. Patients' neurologists gave written confirmation of the MS diagnosis. Finally, the use of psychotherapy and/or

psychotropic medication since baseline assessment was registered, and satisfaction of received care and text messages (if applicable) was measured with the Client Satisfaction Questionnaire (CSQ) and evaluative questions using Visual Analogue Scale (VAS). Adverse events were assessed post hoc by deterioration (increase in significant depression severity; exceeding the lower threshold for suicidal ideation: score > 1 on BDI-II item 9) and non-response (no clinically significant change or deterioration).[11,15] More extensive information can be found in the protocol.[13]

Sample size

The power calculation was based on the comparison of T1 to T0 between the two groups. To demonstrate moderate effects (Cohen's $d = 0.5$) on the primary outcome measure (depressive symptoms), while using a power 0.80, with alpha set at 0.05 (two-tailed), a total set of $n = 64$ patients was needed in each condition. Taking into account an anticipated dropout percentage (about 25%), at least 166 patients had to be included to certify sufficient power.[13]

Randomization and blinding

Patients were randomized by an independent researcher after baseline, using a blocked randomization scheme. A randomly allocated number of patients who took part in the intervention received four weekly supportive text messages on their mobile phones aimed to enhance treatment adherence. Text messages were in addition to the email support that was received by every patient in the IPST group. Patients were informed about their assignment by the first author (R.E.S.). Due to the nature of the intervention, neither patients nor providers of support could be blinded for the intervention. Randomization and statistical analysis were performed blindly.

Statistical analyses

Analyses were based on the intention-to-treat principle. *T*-tests and chi-square tests were used to investigate baseline differences in demographic and clinical variables between both arms. Linear mixed model (LMM) analyses were conducted through a marginal model to evaluate the difference in depressive symptoms (primary outcome) and secondary outcomes between the IPST group and wait list control. LMM analysis is able to handle missing data due to dropout under the assumption that missing data are missing at random.[16] We used an LMM analysis due to progressive insight and deviated from the statistical method described in our protocol (last observation carried forward method and regression imputation). Furthermore, a subgroup analysis was performed using the same procedure as in the intention-to-treat analyses with patients who fulfilled criteria for treatment adherence (at least three modules completed). Cohen's[17] formula was used to calculate effect sizes for the estimated differences.[18] The standardized method of Jacobson and Truax[19] was used to determine clinically significant improvement, deterioration, and recovery. Recovery was defined as reliable change plus a score of 13 or lower on the BDI-II.[14] Finally, descriptive statistics and a chi-square test were used to explore the feasibility of text messages as a way to increase compliance to the intervention. Data were analyzed using IBM SPSS statistics version 20.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA).

Results

Patients

From July 2011 to August 2015, 495 MS patients were assessed for eligibility, of whom, 171 were randomized to IPST ($n = 85$) or wait list control ($n = 86$) (Figure 1). In all, 19 patients (11%) did not complete T1—11 patients in the IPST group and 8 patients in the wait list control. At T2, another $n = 21$ (12%) patients dropped out, leaving $n = 64$ (75%) patients in the IPST group and $n = 67$ (78%) in the wait list control. Dropout rates were not differential with respect to IPST versus wait list control at T1 ($p = 0.449$) and T2 ($p = 0.687$). Average time of T1 was 9 weeks (IPST; 9.1 ± 2.6/wait list control; 9.2 ± 2.5). Baseline demographics and clinical characteristics were much the same between the IPST group and wait list control and are displayed in Table 1.

Differences in baseline characteristics were assessed for patients who completed T1 and those who did not. Non-completers had a higher mean BDI-II score (30.6 ± 7.3 versus 27.3 ± 6.3; $p = 0.035$) and were more often taking anti-depressant medication (16% versus 13%; $p = 0.032$).

Adherence

A total of 57 out of 85 patients (67%) completed at least three modules and were considered treatment completers (mean number of modules for treatment completers was 4.58 ± 0.78 versus 1.07 ± 0.77 for non-completers). Treatment completers had a lower mean age than non-completers (46.2 ± 10.4 versus 52.9 ± 11.3; $p = 0.008$) but did not differ in gender, education level, disability level, and depression severity at baseline. Main reasons for dropout were

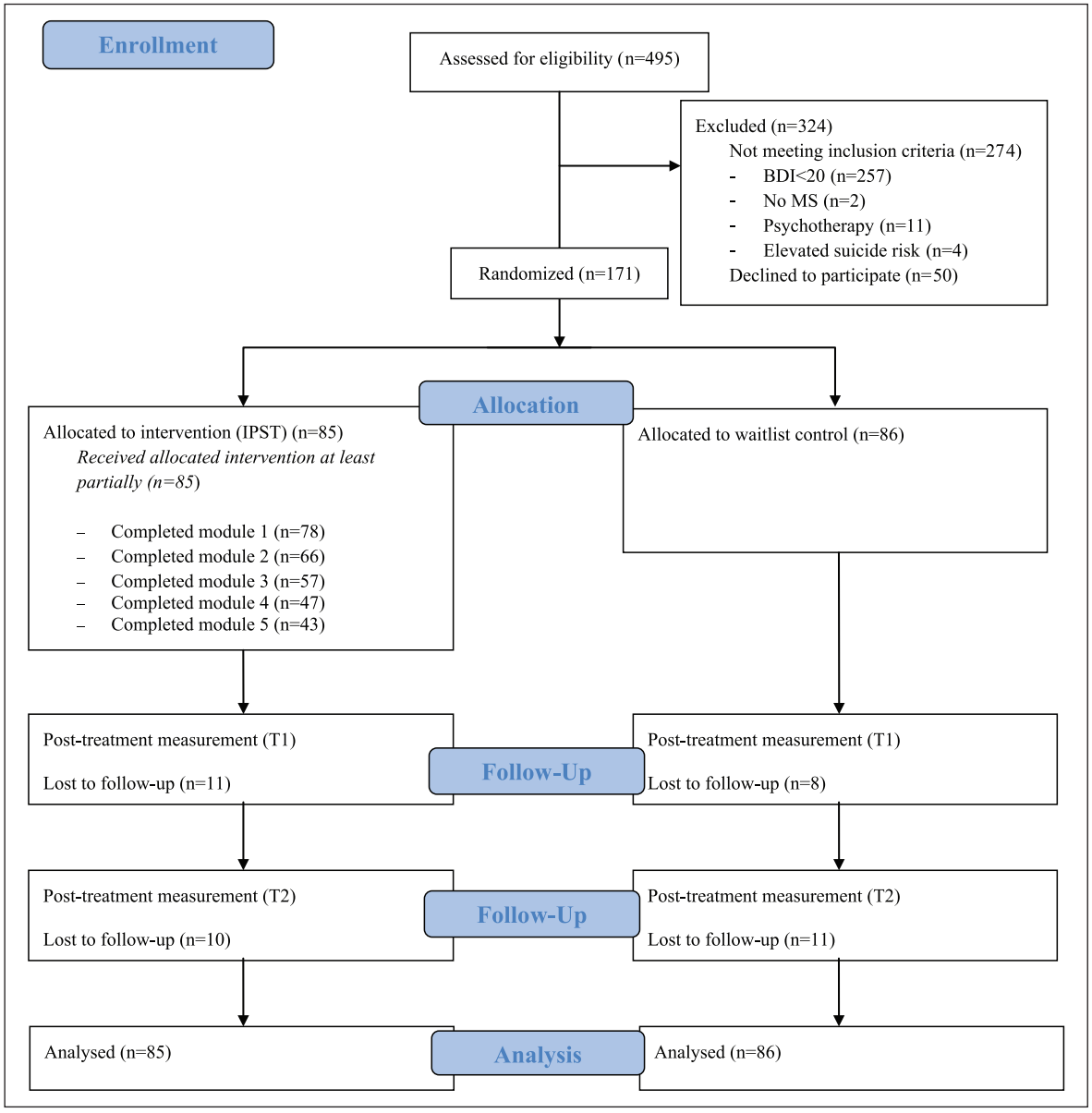

Figure 1. Flow diagram.

computer-related problems ($n=5/28$), lack of time ($n=7/28$), the intervention not meeting patients' needs/starting other treatment ($n=11/28$), MS-related problems such as pain, vision problems, or hospitalization ($n=5/28$).

In total, 40 patients in the IPST arm were allocated to receive additional text messages. Four patients refused these text messages (unfamiliar with/no mobile phone ($n=2$) or not useful ($n=2$)). Additional text messages did not increase the compliance rate of the intervention (three or more modules completed) compared with no text messages (65% versus 69%; $p=0.703$).

Healthcare use

From baseline to T1, there was no difference in healthcare use between the IPST and wait list control: 18% versus 13% contacted a psychologist or psychiatrist ($p=0.414$), and 15% versus 17% used antidepressants ($p=0.258$).

Effects

Improvement on outcome measures. Results of the intention-to-treat analyses are displayed in Tables 2 and 3. A high within-group effect size was found for the primary outcome of depressive symptoms for IPST ($d=1.18$; 95% confidence interval (CI)=(0.88,

Table 1. Baseline demographics and clinical characteristics.

	All patients ($n=171$)	IPST ($n=85$)	Wait list control ($n=86$)
	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %
Demographics			
Age, years	48.9 (10.5)	48.4 (11.1)	49.4 (9.9)
Gender, women	80.1	83.5	76.7
Country of birth			
The Netherlands	93.6	94.1	93.0
Other	6.4	5.9	7.0
Education[a]			
Low	1.2	0.0	2.3
Middle	53.2	56.5	50.0
High	45.6	43.5	47.7
Marital status			
Relationship, yes	78.4	72.9	83.7
MS characteristics			
Years since MS onset	11.2 (8.1)	11.1 (8.3)	11.3 (8.0)
Type of MS (by neurologist)			
Benign	2.3	3.5	1.2
Relapsing remitting	55.0	54.1	55.8
Secondary progressive	28.1	25.9	30.2
Primary progressive	9.9	9.4	10.5
Relapsing progressive	3.5	4.7	2.3
Missing	1.2	2.4	0.0
EDSS ($n=170$)			
0–1.5	3.5	4.7	2.3
2–4	50.9	48.2	53.5
4.5–6	17.5	18.8	16.3
⩾6.5	27.5	27.1	27.9
Medication			
MS disease-modifying ($n=152$)	32.9	36.5	29.5
MS symptom relief ($n=152$)	52.0	48.6	55.1
Anti-depressants, yes	12.9	11.8	14.0
Diagnoses			
Depressive disorder			
First episode (major depressive disorder (MDD))	58.5	53.4	63.3
Current depressive disorder	55.0	56.5	53.5
MDD	52.0	50.6	53.5
Dysthemia	2.9	5.9	0.0
Lifetime depressive disorder (MDD and/or dysthemia)	71.3	72.9	69.8
Anxiety disorder			
Current	31.8	30.6	32.9
Lifetime	41.2	35.3	47.1
Comorbid depressive and anxiety disorder			
Current	20.1	18.8	21.4
Lifetime	32.9	28.2	37.6
Symptom severity			
Depression (BDI-II)	27.7 (6.4)	28.2 (6.6)	27.3 (6.3)
Anxiety (HADS)	10.4 (3.2)	10.4 (3.2)	10.5 (3.2)

IPST: Internet-based problem-solving treatment; MS: multiple sclerosis; EDSS: Expanded Disability Status Scale: 0–1.5 = no complaints, 2–4 = low-to-moderate complaints, 4–6 = moderate-to-severe complaints, ⩾6.5 = very severe complaints; BDI-II: Beck Depression Inventory Second Edition; HADS: Hospital Anxiety and Depression Scale; SD: standard deviation.

[a]Low: primary education, middle: lower general secondary education, intermediate vocational education or high school, high: higher vocational education or university.

Table 2. Mean scores for primary and secondary outcomes for the IPST group at T0 ($n=85$), T1 ($n=74$), and T2 ($n=64$) and the wait list control at T0 ($n=86$), T1 ($n=78$), and T2 ($n=67$).

		IPST	Wait list control
		Mean (SD)	Mean (SD)
Primary outcome			
Depression (BDI-II)	T0	28.2 (6.3)	27.2 (6.6)
	T1	20.3 (8.8)	21.0 (9.1)
	T2	20.8 (10.4)	20.1 (9.2)
Secondary outcomes			
Anxiety (HADS-A)	T0	10.4 (3.2)	10.4 (3.2)
	T1	9.0 (3.8)	9.3 (3.8)
	T2	8.8 (3.8)	8.9 (3.8)
Anxiety (BAI)	T0	18.4 (8.8)	18.5 (0.9)
	T1	15.7 (9.0)	17.4 (11.1)
	T2	16.3 (10.1)	17.1 (11.0)
Fatigue (FSS)	T0	5.8 (1.0)	5.8 (0.9)
	T1	5.7 (0.9)	5.7 (0.9)
	T2	5.7 (1.0)	5.6 (1.1)
Cognitive functioning (MSNQ)	T0	30.6 (10.9)	31.0 (10.1)
	T1	28.7 (10.5)	29.7 (10.0)
	T2	28.0 (10.4)	29.2 (9.8)
Physical and psychological impact of MS (MSIS-29)	T0	89.8 (22.8)	87.6 (21.1)
	T1	82.9 (22.8)	82.6 (23.3)
	T2	84.6 (25.0)	82.6 (32.2)
Quality of life (EQ-5D)	T0	0.47 (.3)	0.51 (.3)
	T1	0.52 (.3)	0.58 (.3)
	T2	0.46 (.4)	0.57 (.3)
Quality of life (EQ-VAS)	T0	57.7 (17.8)	58.1 (17.8)
	T1	59.1 (17.9)	59.9 (17.4)
	T2	58.0 (19.5)	60.4 (18.2)
Problem-solving skills (SPSI-R npo)	T0	19.2 (7.8)	19.4 (7.4)
	T1	15.7 (7.3)	16.8 (7.6)
	T2	17.5 (7.0)	17.1 (7.3)
Problem-solving skills (SPSI-R ppo)	T0	9.4 (3.6)	9.4 (3.4)
	T1	10.1 (3.5)	9.6 (3.4)
	T2	9.5 (3.4)	10.3 (3.5)
Problem-solving skills (SPSI-R av)	T0	10.6 (5.9)	11.1 (5.5)
	T1	8.8 (6.0)	10.3 (5.8)
	T2	10.2 (6.2)	10.1 (5.1)
Mastery (Pearlin Mastery Scale)	T0	13.1 (3.7)	13.1 (3.5)
	T1	13.6 (3.6)	13.4 (3.7)
	T2	12.6 (4.0)	14.1 (4.5)

IPST: Internet-based problem-solving treatment; BDI-II: Beck Depression Inventory Second Edition; HADS-A: Hospital Anxiety and Depression Scale–Anxiety subscale; BAI: Beck Anxiety Inventory; FSS: Fatigue Severity Scale; the scale ranged from 1 (strongly disagree with the statement) to 5 (strongly agree with the statement) instead of 1 (strongly disagree with the statement) to 7 (strongly agree with the statement) and was therefore recoded (1=1; 2=2.5; 3=4; 4=5.5; 5=7); MSNQ: Multiple Sclerosis Neuropsychological Questionnaire; MSIS-29: Multiple Sclerosis Impact Scale-29; EQ-5D: EuroQol quality of life measure; EQ-VAS; EuroQol quality of life measure–Visual Analogue Scale; SPSI-R: Problem Solving Inventory-Revised; npo: negative problem orientation scale; ppo: positive problem orientation scale; av: avoidance scale; SD: standard deviation.

1.47)) and wait list control ($d=0.95$; 95% CI=(0.67, 1.23)) at T1, and for IPST ($d=1.11$; 95% CI=(0.78, 1.43)) and wait list control ($d=1.12$; 95% CI=(0.80, 1.44)) at T2. No significant difference between groups was found at T1 ($d=0.23$; 95% CI=(−4.03, 1.08); $p=0.259$) or at T2 ($d=0.01$; 95% CI=(−2.80, 2.98);

Table 3. Test statistics and effect sizes of the differences in primary and secondary outcomes between the IPST group and wait list control, from linear mixed model analyses.

		t	*p*-value	Effect size (*d*)
Primary outcome				
Depression (BDI-II)	Condition * T1	−1.133	0.259	0.23
	Condition * T2	0.060	0.953	0.01
IPST completers ($n=57$)	Condition * T1	−1.501	0.136	0.34
	Condition * T2	−0.218	0.828	0.05
Secondary outcomes				
Anxiety (HADS-A)	Condition * T1	−0.743	0.458	0.11
	Condition * T2	−0.298	0.766	0.05
Anxiety (BAI)	Condition * T1	−1.654	0.100	0.20
	Condition * T2	−0.260	0.795	0.04
Fatigue (FSS)	Condition * T1	−0.976	0.331	0.17
	Condition * T2	0.502	0.617	0.12
Cognitive functioning (MSNQ)	Condition * T1	−0.611	0.542	0.06
	Condition * T2	−0.358	0.721	0.04
Physical and psychological impact of MS (MSIS-29)	Condition * T1	−0.360	0.719	0.03
	Condition * T2	0.395	0.694	0.00
Quality of life (EQ-5D)	Condition * T1	−0.932	0.353	0.13
	Condition * T2	−1.686	0.094	0.29
Qualty of life (EQ-VAS)	Condition * T1	−0.255	0.799	0.04
	Condition * T2	−0.507	0.613	0.09
Problem-solving skills (SPSI-R npo)	Condition * T1	−1.132	0.259	0.14
	Condition * T2	−0.159	0.874	0.02
Problem-solving skills (SPSI-R ppo)	Condition * T1	0.772	0.441	0.10
	Condition * T2	0.251	0.802	0.20
Problem-solving skills (SPSI-R av)	Condition * T1	−1.385	0.168	0.16
	Condition * T2	0.466	0.642	0.06
Mastery (Pearlin Mastery Scale)	Condition * T1	0.670	0.504	0.09
	Condition * T2	−2.294	0.023	0.34

IPST: Internet-based problem-solving treatment; BDI-II: Beck Depression Inventory Second Edition; HADS-A: Hospital Anxiety and Depression Scale–Anxiety subscale; BAI: Beck Anxiety Inventory; FSS: Fatigue Severity Scale; the scale ranged from 1 (strongly disagree with the statement) to 5 (strongly agree with the statement) instead of 1 (strongly disagree with the statement) to 7 (strongly agree with the statement) and was therefore recoded (1 = 1; 2 = 2.5; 3 = 4; 4 = 5.5; 5 = 7); MSNQ: Multiple Sclerosis Neuropsychological Questionnaire; MSIS-29: Multiple Sclerosis Impact Scale-29; EQ-5D: EuroQol quality of life measure; EQ-VAS; EuroQol quality of life measure–Visual Analogue Scale; SPSI-R: Problem Solving Inventory-Revised, npo: negative problem orientation scale; ppo: positive problem orientation scale; av: avoidance scale.

$p=0.953$) (Figure 2). Also, no significant difference was found when comparing IPST completers ($n=57$; greater than or equal to three modules) with the wait list control at T1 ($d=0.34$; 95% CI = (−5.06, 0.693); $p=0.136$) or at T2 ($d=0.05$; 95% CI = (−3.51, 2.81); $p=0.828$). BDI-II post hoc analyses showed no significant differences between IPST and the wait list control at T1 and T2 in subscale scores and for severely depressed patients versus moderate depressed patients (supplementary material).

For the secondary analyses, there was a difference between the two groups at T2 for mastery ($d=0.34$; $t(169)=-2.294$; $p=0.023$) in favor of the wait list control which should be interpreted, however, as a negligible finding due to multiple testing. No other significant differences were found between groups at different time points.

Clinical significant improvement and recovery. Based on the reliable change index (at least 5-point decrease in the BDI-II),[19] 66% (=49/74) in the IPST group and 53% (=41/78) in the wait list control showed a significant improvement in depressive symptoms at T1 ($p=0.087$) and 63% (40/64) versus 60% (40/67) at T2 ($p=0.743$). In the IPST group, 24% (=18/74) was

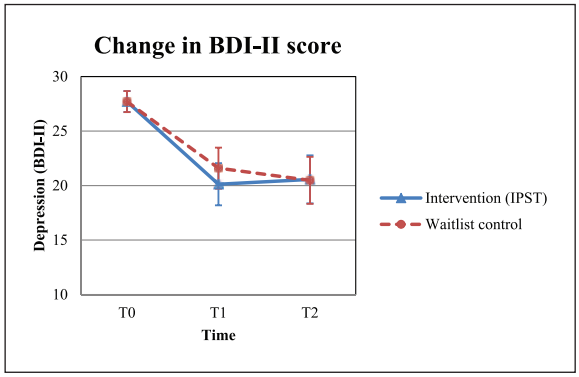

Figure 2. Depressive symptoms for the intervention group (IPST = Internet-based problem-solving treatment) and wait list control at baseline (T0), T1 (after the intervention), and T2 (4 months follow-up).

recovered from depressive symptoms at T1 versus 18% (=14/78) in the wait list control which did not differ significantly ($p = 0.335$). At T2, 28% of patients (=18/64) were recovered in the IPST group versus 26% (=17/67) in the wait list control ($p = 0.722$).

Satisfaction and adverse events

In line with positive evaluations of other ICBT,[8,20] the majority of IPST patients ($n = 73$) were satisfied (as measured with the CSQ) with the help they had received (89%) and would recommend this kind of treatment to others (71%). A total of 80% rated the quality of the intervention as good or excellent, and the majority thought that the intervention helped them to deal with their problems (66%). The website was rated with an average of 7.2 ± 1.3 on a 10-point VAS, and most patients indicated that the website was clear (74%) and easy to use (77%). The majority was satisfied with the frequency of the feedback (85%) and rated its quality as good or excellent (78%).

We found no evidence of adverse events as a consequence of IPST. Post hoc analyses showed no significant difference with regard to the proportion of patients reporting significant deterioration for IPST (7/74) compared with the wait list control at T1 (5/78; $p = 0.486$). The threshold for suicidal ideation was met by one patient in the IPST group and two patients in the wait list control. Non-response was not significantly different for IPST (34%; 25/74) versus the wait list control (47%; 37/78).

Discussion

MS patients with moderate or severe depression treated with guided IPST showed a large decrease in depressive symptoms that sustained over 4 months follow-up. A similar improvement was observed in the wait list control. Therefore, we found no indication that IPST is more effective than a waiting list.

Our findings contrast the result of a study executed in Germany showing effectiveness of ICBT (Deprexis) for depression in MS.[11] Both interventions studied are based on the principles of CBT. "Minder Zorgen" consisted of five sequential modules of problem-solving therapy (PST) with guided email support, whereas the fully automated "Deprexis" offers 9-week access to 10 modules with other CBT techniques next to problem solving. However, within-group effect sizes found for both interventions were substantial (medium for "Deprexis," large for "Minder Zorgen"), suggesting explanations for different between-group findings should not be attributed to the intervention per se.

The considerable decrease in depressive symptoms in our wait list control was unexpected and does not correspond with findings from (I)CBT trials for depression in MS[5,11] or with literature on ICBT for depression in general.[8] Our findings of significant improvement in both arms, including the wait list control, resemble outcomes of several studies comparing ICBT with a wait list control for depressed outpatients, employees, or patients in a community sample.[21–24] Our results were unexpected, and various explanations can be suggested.

First, clarification of our findings is unlikely to be found in the chosen study design, as the use of wait list controls often results in largest trial effect sizes.[25] In addition, we performed a high-quality trial with independent randomization and intention to treat analyses. The large number of participating patients and low dropout rates (11%) are major strengths of our study. Second, our tested intervention is considered sufficient; the decrease in depressive symptoms in the intervention group was as expected, and improvement and satisfaction rates correspond to similar studies and our pilot.[10,20] However, participants had moderate or severe depressive symptoms, where most ICBT studies have focused on mild-to-moderate depression.[8,11,20] Although ICBT for more severely depressed is still a field to explore,[8,20] previous findings suggest that more severely depressed could benefit as much from low-intensity interventions or ICBT as less severely depressed[10,26,27] which is also supported by our post hoc analysis. Third, decreased depressive symptoms could be MS related, as the BDI may measure symptoms of the physical condition along with symptoms of depression. However, most of these symptoms are unlikely to change significantly over the course of a relatively short period, and the BDI is suggested to be an adequate measure for depression in MS.[3,28] Also,

post hoc analyses showed no difference in BDI-II subscale outcomes between groups over time. Fourth, another explanation for improvement in the wait list control might be recruitment of highly motivated patients (the majority of patients applied themselves) who are willing to address their complaints, resulting in improvement accordingly. Even a small degree of contact with a clinician (e.g. interview) seems to lead to better (treatment) outcomes.[29] Fifth, around 15% of patients in both arms received mental healthcare outside our trial which could have affected results. Outcomes for completers receiving no other mental healthcare between baseline and T1 and T2 were therefore additionally compared. Large improvement in depressive symptoms in the IPST group and wait list control remained, and no significant differences were observed (supplementary material). Finally, decreased depression symptomatology in the wait list control could be a result of regression to the mean as high scores are more likely to decrease. It may represent the natural course of depressive symptoms in MS patients. In the general population, half of depressed patients recover within 3 months,[30] which may also apply to the MS population stressing the importance to distinguish between adaptive (negative) emotions that improve over time and persisting emotional disorders with a need for treatment in this patient group.

Altogether, instead of an effect of the intervention, results showed an effect over time in both arms which should probably not be attributed to the study design, depression severity and assessment, or additional care. We feel that the explanation should be sought in spontaneous recovery of a highly motivated subsample of patients. ICBT may be a helpful intervention for depressed MS patients, but it probably has no added value in a select group of motivated patients. As findings on ICBT for depression in MS are inconsistent, more research is advised.

Even though large effect sizes were found within the two arms, around 75% of patients were not recovered at T1 and T2. Non-recovery may be due to high depression severity at baseline,[26,30] to low-intensity treatment, or might have to do with the MS-related depression itself that is suggested to be static[31] and more difficult to treat.[32] If MS-related depression is a more complex persistent condition, it is unrealistic to expect recovery from a single intervention, and combined treatment options should be considered.[33] Since persistent residual depressive symptoms increase the risk of relapse and poor functional and psychosocial outcomes,[34] it is essential to further identify and understand non-recovery of depressed MS patients and adjust treatment accordingly.[26,30]

There are several limitations of our study. First, although the clinical interview at baseline is a strength of our study, it was not performed at T1/T2. Consequently, conclusions are based on self-reported depression that may be prone to bias. Second, adherence rates of our intervention were substantially lower compared with face-to-face treatments.[20] Our effort to increase treatment adherence by adding telephone support (text messages) did not lead to the desired effect. Low ICBT adherence rates are a serious point of concern.[35] However, treatment adherence for MS patients was comparable or better compared with other ICBT interventions,[20,23,24] which is encouraging as lower rates could have been expected due to MS-related complaints interfering with treatment.[12]

Further research is thus needed to understand determinants of (I)CBT response, adherence, and (disease-related) characteristic of depressed MS patients who may benefit from it. Potential advantages of combining ICBT with face-to-face treatment should be investigated as well as combinations with other treatments (e.g. medication).[33]

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