Supplementary data 'No sustainable effects of an internet-based relapse prevention program over 24 months in recurrent depression: primary outcomes of a randomized controlled trial '

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Methods

Study design and participants

As not only individuals with depressive episodes in the preceding 5 years are at high risk for relapse/recurrence but also individuals with multiple episodes over a longer period of time [1], we discarded our initial criterion of having experienced at least two depressive episodes within the past 5 years. In our main analysis we examined whether this had an impact on the results.

Randomization and masking

Randomization was planned to be stratified by type of aftercare and number of depressive episodes. However, due to a programming error, simple randomization was undertaken (1:1 ratio) by an independent researcher using computer-generated random numbers with STATA. Serious adverse events were monitored during the interviews but did not occur.

Interventions

The content of M-CT was written by Bockting and Van Valen [2] and built into the E-platform of the Trimbos Institute. Minimal therapist support was administered, i.e., a maximum of four

telephone sessions with a maximum duration of 30 minutes with a licensed clinical psychologist could be booked by the participants, of which two were pre-booked when module two and five were reached. Participants had access to the program for one year and could repeat the modules as often as desired. As part of the treatment, the mood of the participants was monitored twice a month on a scale from one (very sad) to ten (very cheerful) by text or email messages. When a persistent sad mood was present, i.e. scoring below three twice in a row, further steps were undertaken and participants were advised to seek treatment when there were indications for a depressive episode.

Outcomes

Primary outcome

A subset of 50 interviews was rated by four trained interviewers, resulting in an interrater agreement of 0.96, indicating excellent agreement. The fidelity of masking was moderate to good, i.e., the assessors correctly guessed treatment allocation for 56.3% of the assessments.

Statistical analyses

To examine the intervention's effect on the course of depressive symptoms over 24 months, we used Linear Mixed Models (LMM). A random intercept and slope for the participants was added to the model with an unstructured variance-covariance matrix to account for dependency of the repeated assessments within participants. The analysis was performed with the IDS-SR as dependent variable and time as independent variable. A time-squared variable was included because of apparent non-linearity in the rate of change as reported previously [3]. To examine the strength of the effects, effect sizes were reported using Cohen's d. The interaction between

treatment condition and number of previous depressive episodes was examined explicitly by adding product terms in both the Poisson regression and LMM analysis as decided in advance.

Results

Participant flow and characteristics

Figure 1 depicts the participant flow during the trial. A total of 552 potential participants was assessed for eligibility with the SCID-I, of whom 288 were included. Before randomization, 24 participants dropped-out and subsequently 264 participants were randomly allocated to either M-CT added to TAU (n = 132) or TAU alone (n = 132). All participants were included in the Cox regression analysis. In the M-CT arm, 9 participants withdrew immediately after randomization and in the TAU arm 20 (M-CT: 6 because of a lack of time or motivation, 2 because they were not reachable, and 1 because of increased depressive symptoms. TAU: 9 because of a lack of time or motivation, 8 because they were not reachable, and 3 because of increased depressive symptoms). Therefore, 235 participants were followed for more than zero days after randomization. In addition, 24 participants were lost to follow-up during the 24 months of the study. Baseline characteristics in the ITT sample (Table 1) and of the participants with follow-up data (Table 2) were comparable and balanced over the treatment conditions. Gender and severity of the last depressive episode were slightly imbalanced.

Fig. 1 CONSORT flow diagram over the 24 months follow-up.

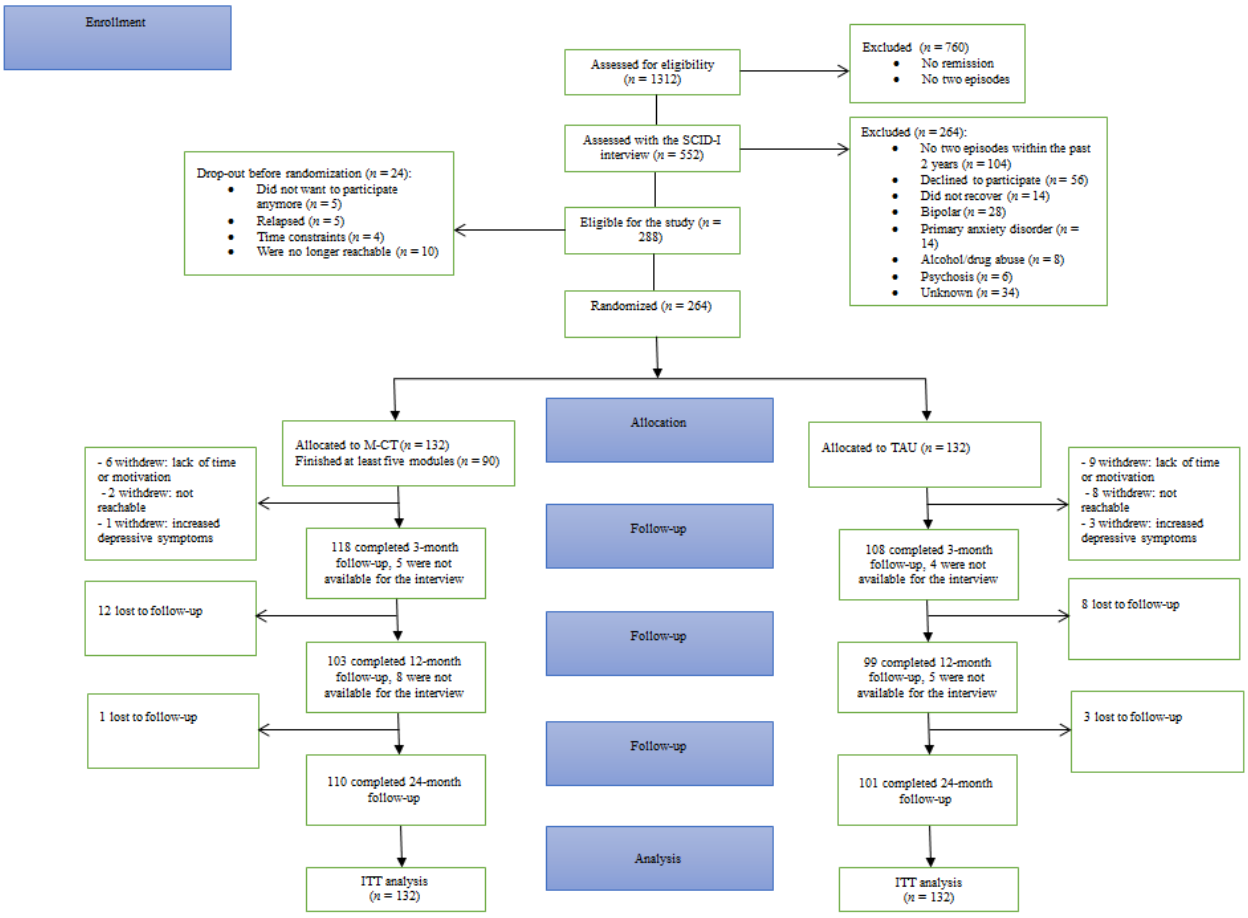


Table 1

Baseline characteristics according to randomized group

Characteristics	M-CT (*n* = 132)	TAU (*n* = 132)
Age, mean (SD)	45.6 (10.9)	47.1 (10.7)
Female gender, % (No.)	79.5 (105/132)	69.7 (92/132)
Country of birth The Netherlands, % (No.)	88.5 (116/131)	92.4 (121/131)
Marital status, % (No.)		
Single	29.8 (39/131)	24.2 (32/132)
Married or cohabiting	62.6 (82/131)	65.9 (87/132)
Divorced/widowed	7.7 (10/131)	9.9 (13/132)
Education, % (No.)		
Primary and/or secondary education	12.9 (17/132)	16.7 (22/132)
Vocational education	22.7 (30/132)	25.8 (34/132)
Higher education	64.4 (85/132)	57.6 (76/132)
Employed, % (No.)	66.4 (87/131)	68.7 (90/131)
Treatment as Usual, % (No.)		
No treatment	34.8 (46/132)	30.0 (39/130)
General practitioner	25.8 (34/132)	33.1 (43/130)
Specialized mental health (after)care	39.4 (52/132)	36.9 (48/130)
Treatment with antidepressant medication	55.4 (72/130)	50.8 (65/128)
Age of first MDD episode, mean (SD)	28.4 (12.1)	30.2 (12.5)
Previous episodes MDD, median (IQR)	4 (2.8)	4 (2.0)
Months in remission, mean (SD)	8.2 (6.5)	8.4 (6.4)

Total HRSD, mean (SD)	3.7 (3.1)	3.4 (2.9)
Depressive symptoms (IDS-SR), mean (SD)	16.5 (10.3)	16.3 (9.7)
Severity past episode, % (No.)		
Mild	28.0 (37/132)	18.9 (25/132)
Moderate	55.3 (73/132)	53.8 (71/132)
Severe	16.7 (22/132)	27.3 (36/132)
Chronic somatic illness, % (No.)	35.4 (45/127)	32.3 (40/124)
Experience with CT, % (No.)	48.3 (57/118)	44.4 (52/117)

Table 2

Baseline characteristics patients with follow-up data

Characteristics	M-CT (*n* = 123)	TAU (*n* = 112)
Age, mean (SD)	45.8 (10.9)	47.9 (10.1)
Female gender, % (No.)	79.7 (98/123)	68.8 (77/112)
Country of birth The Netherlands, % (No.)	87.7 (107/122)	93.7 (104/111)
Marital status, % (No.)		
Single	28.7 (35/122)	23.2 (26/112)
Married or cohabiting	63.9 (78/122)	67.0 (75/112)
Divorced/widowed	7.4 (9/122)	9.8 (11/112)
Education, % (No.)		
Primary and/or secondary education	12.2 (15/123)	16.1 (18/112)
Vocational education	22.0 (27/123)	27.7 (31/112)
Higher education	65.9 (81/123)	56.3 (63/112)
Employed, % (No.)	67.2 (82/122)	67.6 (75/111)
Treatment as Usual, % (No.)		
No treatment	35.0 (43/123)	29.5 (33/112)
General practitioner	25.2 (31/123)	34.8 (39/112)
Specialized mental health (after)care	39.8 (49/123)	35.7 (40/112)
Treatment with antidepressants	55.4 (67/121)	54.5 (60/110)
Age of first MDD episode, mean (SD)	28.2 (12.1)	29.6 (12.2)
Previous episodes MDD, median (IQR)	4 (3.0)	4 (2.0)
Months in remission, mean (SD)	8.2 (6.5)	8.8 (6.5)

Total HRSD, mean (SD)	3.7 (3.1)	3.5 (2.9)
Depressive symptoms (IDS-SR), mean (SD)	16.3 (9.9)	16.2 (9.3)
Severity past episode, % (No.)		
Mild	27.6 (34/123)	16.0 (18/112)
Moderate	57.7 (71/123)	53.6 (60/112)
Severe	14.7 (18/123)	30.4 (34/112)
Chronic somatic illness, % (No.)	33.9 (40/118)	34.9 (38/109)
Experience with CT, % (No.)	48.7 (55/113)	44.2 (46/104)

Primary analysis

When adding a variable in the model that indicated whether both previous depressive episodes occurred in the preceding 5 years to examine whether our changed inclusion criteria had an impact on the results, we found comparable results. In addition, two post-hoc analyses in which we controlled for the number of months in remission and a change in TAU (no change, increase, decrease, or intermittent use) yielded comparable results on our primary outcome (HR = 0.75, 95% CI = 0.51-1.01, p = 0.141; HR = 0.88, 95% CI = 0.58-1.34, p = 0.562 respectively).

Sensitivity analyses

Gender and severity of the last depressive episode were slightly unbalanced over treatment conditions. As studies show that gender is not consistently associated with relapse/recurrence but severity of a depressive episode might be [4], we only controlled for severity of the last depressive episode in the Cox regression analysis. The results were comparable regarding treatment condition (HR = 0.78, 95% CI = 0.52-1.15, p = 0.204) and the interaction between

treatment condition and number of previous depressive episodes (HR = 0.72, 95% CI = 0.33-1.57, p = 0.408), chronic somatic illness (HR = 0.58, 95% CI = 0.25-1.31, p = 0.186), and TAU (HR = 0.90, 95% CI = 0.58-139, p = 0.622).

The analysis in the per protocol sample, including the participants that finished at least five modules (n = 222), yielded comparable results (treatment condition alone: HR = 0.85, 95% CI = 0.57-1.29, p = 0.451; interaction treatment condition and number of previous depressive episodes: HR = 0.68, 95% CI = 0.31-1.51, p = 0.344; chronic somatic illness: HR = 0.73, 95% CI = 0.31-1.73, p = 0.475; and TAU: HR = 0.78, 95% CI = 0.49-1.25, p = 0.300).

In order to test the robustness of the primary analyses, multiple imputation with fully conditionally specified models and predictive mean matching was performed. Multiple imputation reduces the chance of bias and allows use of all data available in the analyses, which optimizes statistical power [5]. The imputed datasets were combined according to Rubin's rules [6]. Multiple imputation is only valid if the missing at random assumption holds, which cannot be proved. To substantiate this assumption, a logistic regression analysis was performed in which we examined if baseline characteristics predicted whether the data was missing. This resulted in a statistical significant model ($X^2(25) = 44.19$, p = 0.010), suggesting the data were at least partly missing at random and multiple imputation would improve the validity of the analyses. When the Cox regression analyses were repeated using multiple imputation, the results were comparable regarding treatment condition (HR = 0.81, 95% CI = 0.56-1.17, p = 0.256) and the interaction between treatment condition and number of previous depressive episodes (HR = 0.95, 95% CI = 0.47-1.94, p = 0.897, chronic somatic illness (HR = 0.68, 95% CI = 0.31-1.50, p = 0.342), and TAU (HR = 0.90, 95% CI = 0.60-1.36, p = 0.613).

Secondary analyses

In the M-CT condition 20.9% experienced one relapse/recurrence and 21.8% more than one during the 24-month follow-up. In the TAU condition 24.8% experienced one depressive episode and 23.8% more than one. In the Poisson regression analysis, no interaction was found between treatment and number of previous depressive episodes (IRR = 1.22, 95% CI = 0.64-2.31, p = 0.543).

Table 3 shows the results of the LMM analyses that examined the course of depressive symptoms measured with the IDS-SR. Figure 3 shows that until approximately 9 months, depressive symptoms seem lower in the M-CT condition and subsequently this effect reverses.

Table 3

Estimated change (linear mixed models) in depressive symptoms over 24 months

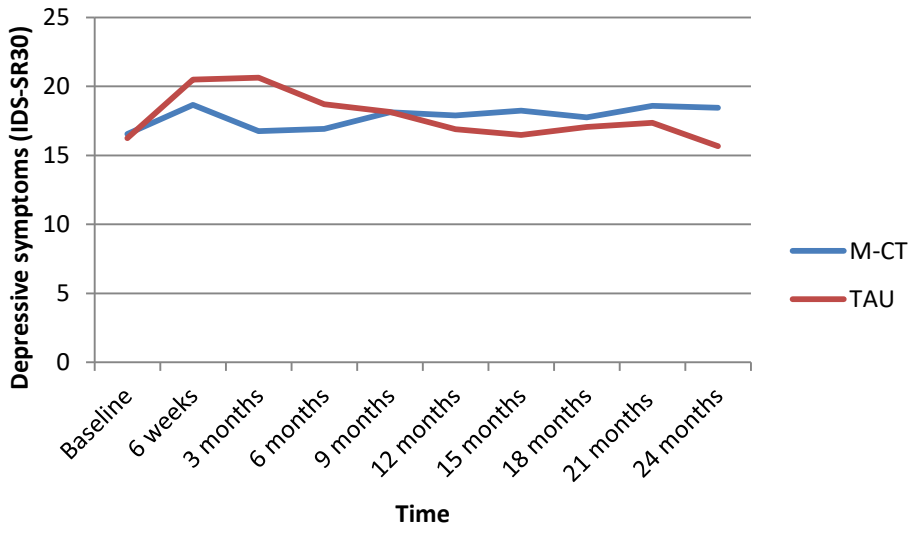
	Estimate (95% CI)	*P*	Cohen's d (95% CI)
Intention to treat (*n* = 264)			
Time*treatment	0.31 (-0.09 to 0.70)	0.131	0.03 (-0.01 to 0.068)
Time*treatment*episodes[a]	-0.03 (-0.57 to 0.51)	0.910	-0.01 (-0.06 to 0.06)

Depressive symptoms were assessed with the Inventory of Depressive Symptomatology Self-Report.

[a]Episodes = number of previous depressive episodes measured at baseline.

Fig. 3

Mean levels of depressive symptoms during 24 months follow-up in M-CT (*n* = 129) and TAU (*n* = 128)



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