Effect of sleep disturbance symptoms on treatment outcome in blended CBT for depression: A secondary analysis of the E-COMPARED study.

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Abstract

Background: Sleep disturbance symptoms (SDS) are common in major depressive disorder (MDD) and have been found to hamper the treatment effect of conventional face-to-face psychological treatments such as cognitive behavioral therapy (CBT). To increase the dissemination of evidence-based treatment, blended CBT (bCBT) consisting of online and face-to-face treatment is on the rise for MDD patients. To date, no study has examined whether SDS has an impact on bCBT treatment outcomes and whether it affects bCBT and treatment as usual (TAU) equally.

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Methods: The study was based on data from the E-COMPARED study: a two-arm, multisite, parallel randomized controlled, non-inferiority trial. A total of 943 MDD outpatients were randomized to either (1): bCBT (n=476) or (2): TAU consisting of routine clinical MDD treatment (n=467). The primary outcome for the present study was the change of depression symptom severity at 12-months follow-up. Secondary outcomes were the change of depression symptom severity at 3- and 6-months follow-up and MDD diagnoses at 12-months follow-up, assessed with the Patient Health Questionnaire-9 (PHQ-9) and Mini-International Neuropsychiatric Interview (MINI), respectively. Mixed effects models were used to examine the association of SDS with treatment outcome and treatment modality over time.

Results: 558 of the 943 (59.17%) patients recruited for the study completed the 12-months follow-up assessment. On the total sample, baseline SDS did not significantly affect change in depressive symptom severity at twelve months follow-up (ß = .16, 95% CI [-.04, .36]). However, baseline SDS were negatively associated with treatment outcome for bCBT (ß = .49, 95% CI [.22, .76]) but not for TAU (ß = -.23, 95% CI [-.50, .05]) at 12-months follow-up, even when adjusting for baseline depression symptom severity. The same picture was seen for the effect of SDS on the presence of depression measured with MINI at 12-months follow-up. However, for both treatment formats baseline SDS were not associated with depression symptom severity at neither 3- (ß = .06, 95% CI [-.11, .23]) nor 6-months (ß = .09, 95% CI [-.10, .28]) follow-up.

Conclusions: Baseline SDS may have a negative impact on long-term treatment outcomes in bCBT for MDD. This effect was not present for TAU. These findings suggest that special attention to SDS might be warranted when MDD is treated with bCBT. Future studies should investigate the effect of implementing modules specifically targeting SDS in bCBT for MDD to improve the long-term prognosis. Clinical Trial: ClinicalTrials.gov: France: NCT02542891; Poland: NCT02389660; Spain: NCT02361684; Sweden: NCT02449447; Switzerland: NCT02410616; other clinical databases: Germany: German Clinical Trials Register DRKS00006866; The Netherlands: Netherlands Trials Register NTR4962; United Kingdom: ISRCTN registry, ISRCTN12388725; Denmark: ClinicalTrials.gov NCT02796573

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Keywords: blended care, bCBT, cognitive behavioral therapy, digital intervention, major depressive

disorder, sleep disturbance, sleep disorder

Introduction

Major depressive disorder

Major depressive disorder (MDD) is among the most prevalent and debilitating psychiatric disorders [1-3], and it has been estimated to be the third leading cause of disability worldwide [3]. The MDD burden is particularly prominent in Western societies and poses an immense burden on society [1,3,4]. Although MDD, in many cases, can be successfully treated with evidence-based psychological and pharmacological therapies [5], some patients do not respond to treatment or do not receive adequate treatment [6]. To alleviate the burden of the disorder, we need to understand the mechanisms that may impact the lack of treatment response and develop strategies for broader dissemination of evidence-based psychological treatments [5,7].

Depression and sleep disturbance

MDD is a heterogeneous condition with a variety of presentations and a broad constellation of associated symptoms. Sleep disturbances are core symptoms of MDD, covering mostly insomnia (difficulties falling asleep, wakefulness after sleep onset, and/or waking up early and not being able to get back to sleep), but to a lesser extent also hypersomnia (excessive daytime sleepiness and/or excessive total sleep time) [8]. While insomnia and hypersomnia are common symptoms of MDD, they might also be diagnosed as independent psychiatric disorders [9]. Insomnia and mood disorders seem to have a bidirectional relationship, with insomnia increasing the risk for MDD, while MDD also increases the risk for insomnia symptoms [8]. This complex relationship seems to be founded in both common predisposing biological factors as well as cognitive and behavioral elements perpetuating both disorders, such as attentional biases and conditioning of arousal and negative affect in the bedroom [10]. Several studies have examined the impact of insomnia on the effect of MDD treatment and have consistently shown that insomnia affects the response to evidence-based treatment for depression, such as cognitive behavioral therapy (CBT) [11-14]. Two studies [12,14] reported that insomnia symptoms may double the risk for non-remission following depression

treatment. In another study, patients exhibiting a limited response to treatment were more likely to present with recurring insomnia and depressive episodes, while optimal responders were consistently lower on insomnia measures [11]. Also, a randomized controlled trial (RCT) on elderly MDD patients found that patients who presented with persistent insomnia symptoms, i.e., reporting symptoms at baseline and 3-months follow-up, were less likely to reach remission at 6- and 12-month time points [13]. Further, insomnia symptoms are among the most frequent residual symptoms following depression treatment [15-17]. Hypersomnia has not received the same attention as comorbid insomnia in MDD, perhaps because it is less common [18]. However, studies have found that persons with MDD who experience both hypersomnia and insomnia are more severely depressed compared with depressed individuals with only insomnia or no sleep disturbance symptoms (SDS) [18,19].

Digital interventions

Digital interventions are often recommended as a tool to increase the dissemination of evidence based psychological treatments [5,7]. Meta-analyses have shown that internet-based, guided self-help CBT (iCBT) is effective for treating depressive symptoms [20,21], and it may allow patients to circumvent some of the financial and structural barriers to psychological treatment [22]. However, iCBT is also affected by SDS. A cohort study on iCBT for depression in routine care, showed that more sleep problems predicted higher depression by the end of treatment [23]. Further, an RCT on iCBT for chronic stress showed that the treatment effect was mediated by the reduction in insomnia symptoms [24]. Interestingly, some studies have shown that iCBT for insomnia also has significant effects on depressive symptoms [25,26], and in some cases studies have also included insomnia management in the iCBT treatment manual for depression [27]. However, the added effect of doing so has yet to be documented.

Since the self-help format in iCBT has a more rigid treatment structure, it might be more challenging to adapt the treatment to the individual's symptom presentation. Standard CBT protocols often do not

target SDS during treatment. However, within the face-to-face consultation, the therapist may have more flexibility to address other issues experienced by the patient. Perhaps even more so in routine care treatments, where therapists are not required to adhere strictly to a protocol as in a research project. The therapist could also favor another treatment approach that emphasizes SDS more than CBT. Digital interventions might lack this flexibility, when some or all of the treatment is delivered in a standardized format with predetermined exercises. One study also showed that while some patients feel empowered and safe in the iCBT format, others do experience isolation and feel burdened by the limited therapist support [28].

Blended cognitive behavioral therapy

Blended CBT (bCBT) might help bridge this gap between online and face-to-face treatment. In bCBT, patients receive a combination of online and face-to-face therapy. This may help therapists and patients adhere to treatment protocols while allowing for a different kind of flexibility during the physical consultations compared with the structured, guided self-help programs [29]. Face-to-face consultations in bCBT can alleviate the feelings of isolation that patients may experience in guided self-help, and it can help make the structured treatment content of CBT relatable and adaptable to the patient's symptom profile [30]. However, no study has yet investigated the impact of SDS on digital interventions for MDD, including bCBT, compared with face-to-face treatments. Since digital interventions are increasingly being offered to patients with MDD to augment the reach of evidence-based treatment, it is relevant to examine the association between the severity of SDS and treatment response to bCBT.

Objectives

The objectives of this study were to investigate: (1) whether baseline sleep disturbance symptoms have a negative impact on treatment outcomes for depression independent of treatment modality, and (2) whether sleep disturbance symptoms impact blended CBT and treatment as usual (TAU) in routine care equally.

Based on prior research, we hypothesized a priori that sleep disturbance symptoms would be negatively associated with treatment outcome independently of treatment modality.

Methods

This study was a sub-study of The European COMPARative Effectiveness research on blended Depression treatment versus treatment-as-usual (E-COMPARED) (described in more detail elsewhere) [31].

The trial was registered in clinical trial databases (*ClinicalTrials.gov*: France: NCT02542891; Poland: NCT02389660; Spain: NCT02361684; Sweden: NCT02449447; Switzerland: NCT02410616; *other clinical databases*: Germany: German Clinical Trials Register DRKS00006866; The Netherlands: Netherlands Trials Register NTR4962; United Kingdom: ISRCTN registry, ISRCTN12388725; Denmark: ClinicalTrials.gov NCT02796573) and was conducted based on the Consolidated Standards of Reporting Trials (CONSORT) [32].

Study Design and Setting

The E-COMPARED trial was conducted as a two-arm, parallel, randomized, controlled, non-inferiority trial in nine European countries: France, Germany, The Netherlands, Poland, Spain, Sweden, Switzerland, the UK, and Denmark.

The trial was conducted in routine primary care (sites: Germany, Poland, Spain, Sweden, and the UK) or specialized mental health care (sites: France, The Netherlands, Switzerland, and Denmark).

Eligibility criteria

To be included in the study, patients had to (1) be aged 18 years or older, (2) fulfill DSM-IV diagnostic criteria for MDD, and (3) exhibit minimal to severe symptoms of depression based on a score of ≥5 on a screening with the Patient Health Questionnaire-9 (PHQ-9) (described in more detail in Section 2.5.1.).

Exclusion criteria were: (1) current high risk for suicide, (2) fulfill DSM-IV diagnostic criteria for

substance dependence, psychotic illness, bipolar affective disorder, or obsessive compulsive disorder, (3) receiving psychological treatment at the time of enrolment for depression in primary or specialized mental health care, (4) being unable to comprehend the spoken and written language of the country where the study is conducted (e.g., English in the UK), (5) not having access to a computer with a fast internet connection, and (6) not having or being willing to carry a smartphone that is compatible with the mobile component of the intervention being offered.

Randomization and blinding

Eligible participants were randomized by a team of independent researchers (the randomization team) affiliated with the PI organization (VU Amsterdam) into two arms: TAU or bCBT. Randomization took place at the individual level, stratified by country. The randomization team created the allocation scheme with a computerized random number generator (Random Allocation Software) at an allocation ratio of 1:1. Block randomization with variable block sizes that varied between 8 and 14 allocations per block was applied.

None of the investigators or clinicians were aware of the randomization scheme but blinding for treatment allocation was not possible due to the nature of the treatment. Nonetheless, the outcome assessors were blinded.

Treatment arms

TAU was defined as the routine care patients received when diagnosed with depression in the specific country and treatment setting where they were recruited. Thus, TAU varied between countries, treatment settings, and among patients and included pharmacologic treatment, psychotherapy, a combination of both or none of the above (see Table 1).

Table 1. Overview of bCBT and TAU applied in each country.

Country	Platform bCBT	Duration	Online/FTF	Sequencing	TAU
Germany	Moodbuster	10-13 weeks	10/5	Alternate	TAU from GP
Sweden	Iterapi	10 weeks	6/4	Alternate	TAU from GP[a]
Netherlands	Moodbuster	20 weeks	10/9	Alternate	FTF TAU[b]

United Kingdom	Moodbuster	11 weeks	5/6	Alternate	FTF CBT
Spain	Smiling is fun[c]	10 weeks	8/3	1-4-1-4-1	TAU from GP
France	Moodbuster	16 weeks	8/8	Alternate	FTF CBT
Switzerland	Deprexis[d]	18 weeks	9/9	Alternate	FTF CBT
Poland	Moodbuster	6-10 weeks	6/7	Alternate	FTF CBT
Denmark	NoDep[e]	12 weeks	6-8/6	Alternate	FTF CBT

[a]Sweden also included psychotherapy clinics and student mental health care facilities. However, these are at the same level of care as GP.
[b]Psychotherapy (CBT, interpersonal psychotherapy (IPT) or supportive therapy), antidepressant medication, running therapy, or a combination of these.
[c]Additional module on coping skills.
[d]Additional modules on mindfulness, interpersonal skills, positive psychology, emotion-focused therapy, childhood experiences.
[e]Two additional modules on restructuring of beliefs and management of rumination that clinicians could add to the online sessions if deemed necessary.
Abbreviations: bCBT: Blended cognitive behavioral therapy; CBT: Cognitive behavioral therapy; FTF: Face-to-face; GP: General practitioner; TAU: Treatment as usual.

The blended depression treatment combined individual face-to-face CBT with CBT delivered through an internet-based treatment platform with mobile phone components (integrated either in the treatment platform or as a separate system). The core components of the bCBT treatment were: (1) psychoeducation, (2) cognitive restructuring, (3) behavioral activation, and (4) relapse prevention. These were delivered over 10–20 sessions. The ratio between the number of face-to-face sessions and the number of online modules varied according to practice in participating countries. However, a minimum of one third of the sessions were face-to-face, and a minimum of one third of the sessions were provided online. In addition to the core CBT components, other components such as mindfulness, coping skills training, or problem-solving could also be included (insomnia management was not included in the present trial). However, they were not allowed to take up more than a quarter of the total treatment (no more than about 25 % of the face-to-face and online sessions combined). This was to prevent too much heterogeneity in the treatment programs.

bCBT was provided by CBT therapists who received training on how to deliver the treatment. CBT therapists were either 1) licensed CBT therapists, 2) CBT therapists in training working under the supervision of an experienced licensed CBT therapist in specialized mental health care, 3) licensed psychologists, or 4) psychologists in training working under the supervision of a licensed psychologist with a CBT orientation in primary care.

As can be seen in Table 1, none of the bCBT-protocols included SDS interventions. However, we do not know to what extent SDS was included in treatment in the TAU-condition.

Measures

Sociodemographic factors, MDD diagnoses, the severity of depressive symptoms, and psychiatric comorbidity were measured at baseline. The clinical outcome measures used in this study were severity of depressive symptoms assessed at baseline and at 3-, 6- and 12-months follow-up and MDD diagnosis assessed at baseline and at 12-months follow-up.

Assessment instruments

MDD severity. The Patient Health Questionnaire-9 (PHQ-9) was used to assess depression severity. It includes symptom domains of MDD based on DSM-IV (i.e., sleep disturbance, sad mood, appetite/ weight, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, psychomotor agitation/retardation). It consists of nine items; each scored on a 0–3 scale, with the total score ranging from 0–27 and higher scores indicating more severe depression [33]. The PHQ-9 is frequently used in clinical trials to assess treatment outcomes and can be used in different patient populations such as primary care and specialized mental health care [34]. The PHQ-9 was used to screen for the presence of at least a minimum level of MDD severity (cut-off ≥ 5). Further, the PHQ-9 total score was applied as the primary outcome. For this study, the 12-months follow-up was used as the primary endpoint. The 3- and 6-months follow-ups were secondary endpoints.

MDD Diagnosis. The Mini-International Neuropsychiatric Interview (MINI) for DSM-IV is a structured interview probing the 17 most common psychiatric diagnoses using dichotomous questions requiring a yes/no response [35]. The MINI was used to establish MDD diagnoses as well as to screen patients for eligibility and detect comorbid psychiatric diagnoses. The MINI was also used to evaluate whether the patients still fulfilled the diagnostic criteria for an MDD diagnoses at 12-months follow-up and was applied as a secondary outcome and secondary endpoint.

Sleep disturbance symptoms. Four sleep disturbance items from the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) were used to measure SDS [36]: 1) Difficulty Falling Asleep, 2) Awake During the Night, 3) Waking Up Too Early, and 4) Sleeping Too Much. Each item scores 0–3, the higher scores, the greater symptom severity. This approach to measure SDS has been validated previously for the three insomnia items [37]. However, the middle answer-categories (scores of 1 and 2) did not perform as well for items 2) and 3) [37]. Therefore, based on prior research, a score of ≥2 on an item was chosen to indicate the presence of that specific type of sleep disturbance [38]. A combination of any (or none) of the four types of SDS was possible.

Analysis plan

Characteristics of the sample at baseline were described using descriptive statistics and compared across groups using t-tests for continuous variables and Chi-square tests for categorical variables. If continuous variables violated the assumption of normality, equivalent nonparametric tests were used (Wilcoxon signed rank test).

The primary analysis was performed using a linear mixed effects model with random intercept [39,40] with sites added as a random variable. The outcome variable was the difference in score on the PHQ-9 between baseline and at 12-months follow-up. The baseline sum score of the first four items on the QIDS-SR pertaining to SDS was used as a predictor variable and was controlled for baseline level of depression severity on the PHQ-9. To test for an effect of treatment modality (bCBT vs. TAU), an interaction term between the SDS and treatment modality was added. A sensitivity analysis excluding item 3 in the PHQ9 (pertaining to sleep disturbance) was also performed as this item could potentially confound the analyses.

Secondary analyses were also conducted with linear mixed effects models applying the same predictor and outcome variables as well as an interaction term, but at 3- and 6-months follow-up. Also, an analysis utilizing the same predictor variable and the presence vs. absence of MDD diagnoses at 12-months follow-up as the outcome was conducted. This analysis was performed using

a logistic mixed effects model.

All models were adjusted for baseline level of depression on the PHQ-9 and sociodemographic variables (gender, marital status, highest education, and age).

All analyses followed intention-to-treat (ITT) principles according to CONSORT guidelines [41]. Missing values were handled by using all available data in mixed effects models. A double-sided significance level of .05 was applied. All calculations were performed using R version 3.6.3 [42]. Linear mixed-effects models were fitted using the lme4 package [40].

Results

The sample consisted of 943 adult MDD patients recruited from routine care across the nine participating European countries. The mean age was 39 (*SD* = 13) years with mainly women included (*n* = 644, 68%). The majority were either married or living together (*n* = 517, 55%) and were well educated. At baseline, the sample, on average, presented with a moderate to severe degree of depression (mean PHQ-9 = 15.35, *SD* = 4.77). There were no differences between the groups on any sociodemographic measures nor on depressive or sleep symptomatology at baseline. Characteristics of the participants are summarized in Table 2.

Table 2. Comparison of characteristics across treatment modalities

	Total Sample	TAU	bCBT	*P*
Sample Size				
n	943	467	476	
Age				
Age, mean (*SD*)	38.96 (13.09)	38.71 (13.08)	39.21 (13.10)	.562
Gender				
Female, mean (*SD*)	644 (68.3)	326 (69.8)	318 (66.8)	.358
Marital Status				
Marital Status *n* (%)				.270
Single	314 (33.3)	155 (33.2)	159 (33.4)	
Divorced	103 (10.9)	43 (9.2)	60 (12.6)	
Widowed	9 (1.0)	6 (1.3)	3 (.6)	
Living Together	206 (21.8)	111 (23.8)	95 (20.0)	
Married	311 (33.0)	152 (32.5)	159 (33.4)	
Highest Education				
Highest Level of Education *n* (%)				.917
Low	146 (15.5)	74 (15.9)	72 (15.1)	
Middle	349 (37.0)	170 (36.5)	179 (37.6)	

High	447 (47.5)	222 (47.6)	225 (47.3)	
Site				
Trial Site *n* (%)				.999
Germany	173 (18.3)	87 (18.6)	86 (18.1)	
Sweden	141 (15.0)	68 (14.6)	73 (15.3)	
Netherlands	102 (10.8)	49 (10.5)	53 (11.1)	
UK	101 (10.7)	52 (11.1)	49 (10.3)	
Spain	127 (13.5)	63 (13.5)	64 (13.4)	
France	105 (11.1)	54 (11.6)	51 (10.7)	
Switzerland	50 (5.3)	24 (5.1)	26 (5.5)	
Poland	84 (8.9)	42 (9.0)	42 (8.8)	
Denmark	60 (6.4)	28 (6.0)	32 (6.7)	
Psychometrics				
PHQ-9, mean (*SD*)	15.36 (4.78)	15.38 (4.66)	15.34 (4.90)	.887
QIDS Sum of Sleep Scores Items 1-4, mean (*SD*)	4.79 (2.42)	4.71 (2.31)	4.87 (2.52)	.312
Insomnia items				
Difficulty Falling Asleep, *n* (%)	453 (48.3)	225 (48.4)	228 (48.3)	1.000
Awake During the Night, *n* (%)	512 (54.7)	251 (54.1)	261 (55.3)	.761
Waking Up Too Early, *n* (%)	321 (34.5)	149 (32.3)	172 (36.7)	.177
Hypersomnia item				
Sleeping Too Much, *n* (%)	135 (14.4)	65 (14.0)	70 (14.9)	.771

Abbreviations: bCBT: Blended cognitive behavioral therapy; PHQ-9: Patient health questionnaire-9; QIDS: Quick inventory of depressive symptomatology; SD: Standard deviation; TAU: Treatment as usual.

In the present sample, 764 (81%) reported at least one symptom of SDS at baseline. The most common symptom of sleep disturbance upon entering the study was mid-nocturnal insomnia (512/943, 54.3%), which was reported by more than half of the participants. In close succession followed sleep onset insomnia (453/943, 48%). Hypersomnia was markedly less prevalent than the rest (135/943, 14.3%).

As measured with the sum of the first four items in the QIDS pertaining to sleep, the level of sleep disturbance reduced over time, as can be seen in Table 3. In Figure 1, the levels of severity of depressive and sleep disorder symptoms are presented for the total sample and for each treatment condition.

Table 3. Observed means of SDS severity

	Total sample *Mean (SD)*	**TAU** *Mean (SD)*	**bCBT** *Mean (SD)*
Baseline	4.79 (2.42)	4.87 (2.52)	4.77 (2.31)
3 months	3.89 (2.43)	3.83 (2.49)	3.94 (2.37)
6 months	3.61 (2.38)	3.52 (2.42)	3.69 (2.33)

12 months	3.28 (2.39)	3.27 (2.46)	3.30 (2.33)

Abbreviations: bCBT = Blended cognitive behavioral therapy, SDS = Sleep disturbance symptoms, TAU = Treatment as usual.

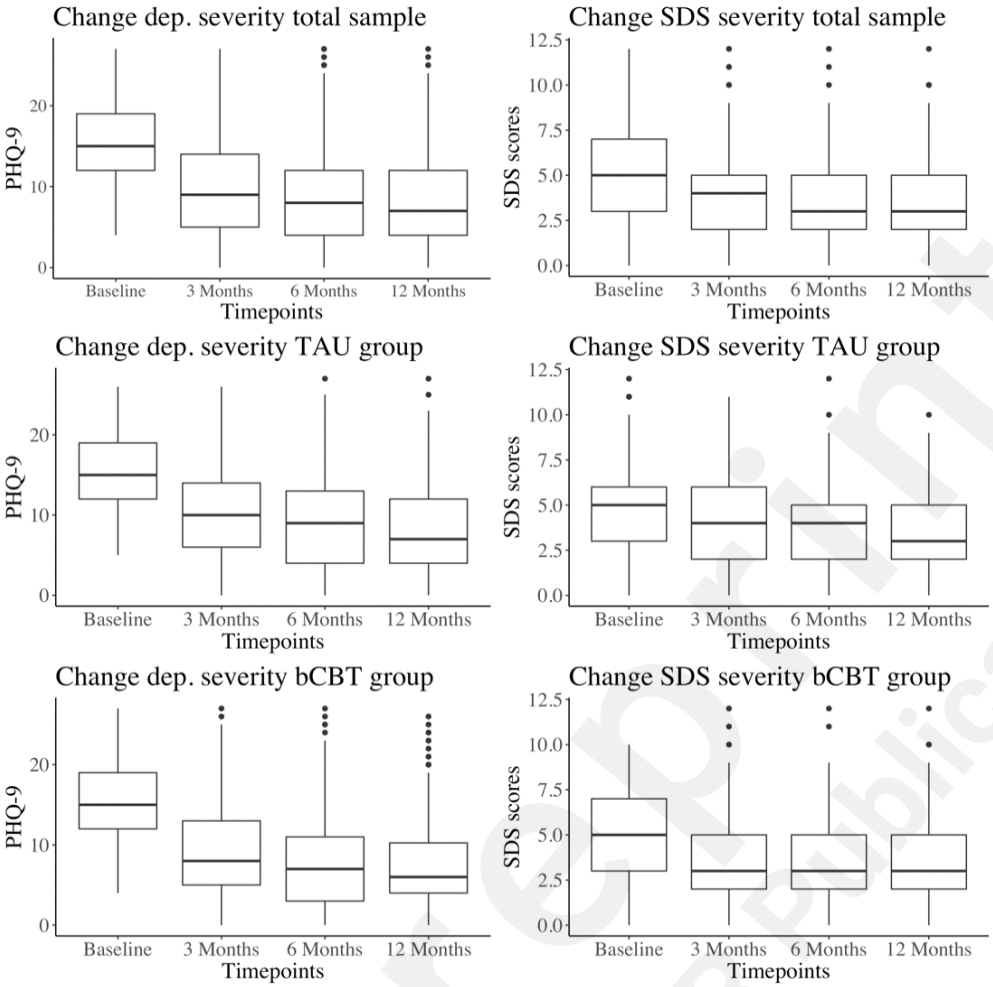

Figure 1. Changes in symptoms severity of depression and SDS from baseline to 12-months follow-up

Abbreviations: bCBT = Blended cognitive behavioral therapy, dep. = depression, PHQ-9 = Patient health questionnaire-9, SDS = Sleep disturbance symptoms.

In the total sample, the level of SDS did not significantly predict the change in depression symptom severity from baseline to 12-months follow-up (*ß* = .16, 95% *CI* [-.04, .36]). However, there was a difference between the groups, with the effect of baseline SDS being non-significant in the TAU group (*ß* = -.23, 95% *CI* [-.50, .05]), but being significant for the bCBT group (*ß* = .49, 95% *CI* [.22, .76]). When including an interaction term with group, the interaction was significant (*ß* = .59, 95% *CI* [.23, .94]), indicating a significant difference in how affected change at 12-months was by baseline SDS between the groups. In a sensitivity analysis, we removed item 3 in the PHQ-9

(pertaining to sleep disturbances), which led to similar results. For this reason, we decided to continue using the full PHQ-9, given that it is the validated version and for the purpose of comparability. The results of the models can be seen in Table 4.

In line with the primary finding, baseline SDS severity did not significantly predict the presence of MDD diagnoses for the total sample as assessed by the MINI MDD module at 12-months follow-up (*OR* = 1.05, 95% *CI* [.96, 1.16]). But again, the effect was significant for the bCBT group (*OR* = 1.18, 95% *CI* [1.02, 1.38]) and not the TAU group (*OR* = .94, 95% *CI* [.82, 1.08]).

Due to the diversity in interventions offered in the comparison group (TAU), we performed the same analyses for a subset of sites, who used face-to-face CBT as the comparator (UK, France, Switzerland, Poland, Denmark). As was the case for all sites, the results of the subgroup were not significant for the total sample (*ß* = .27, 95% *CI* [-.09, .63]) and only the bCBT group showed a significant effect of SDS (*ß* = .69, 95% *CI* [.19, 1.19]). However, the interaction term with group was *in*significant (*ß* = .56, 95% *CI* [-.07, 1.22]). This could be due to the subgroup including fewer subjects, thus widening the confidence interval. Analyses of the presence of depression according to the M.I.N.I. did not result in any significant results, which again might be caused by the smaller sample size.

The effect of SDS on the change in the severity of depressive symptoms was non-significant from baseline to 3- and 6-months follow-up for both treatment formats, suggesting that SDS may not have an effect on short-term treatment gains.

Table 4: Associations between change in depression score and sleep score

	All participants			**Treatment as usual**			**bCBT**		
	Regression coefficient			Regression coefficient			Regression coefficient		
Primary outcome	n	B[a]	Adj. B[b] [95% CI]	n	B[a]	Adj. B[b] [95% CI]	n	B[a]	Adj. B[b] [95% CI]
Change in depression score at 12 months follow-up									
Sleep score at baseline, per 1 unit increase	558	.21	.16 [-.04, .36]	274	.01	-.23 [-.50, .05]	284	.35	.49 [.22, .76]
Difference between treatment conditions									
SDS*condition		.59	.59 [.23, .94]						
Secondary outcomes									

Change in depression score at 3 months follow-up									
Sleep score at baseline, per 1 unit increase	748	.09	.06 [-.11, .23]	379	.12	.07 [-.17, .31]	369	-.07	.07 [-.16, .32]
Change in depression score at 6 months follow-up									
Sleep score at baseline, per 1 unit increase	657	.15	.09 [-.10, .28]	319	.14	.03 [-.25, .32]	338	.16	.12 [-.14, .37]

[a]Adjusted for depression score at baseline
[b]Adjusted for gender, age, marital status, highest education and depression score at baseline
Abbreviations: bCBT = Blended cognitive behavioral therapy, SDS = Sleep disturbance symptoms.

Three of the four items on SDS in the QIDS pertained to insomnia, and one pertained to hypersomnia (see Table 2). Exploratory analyses were performed to examine whether there was a difference between the effect of hypersomnia and insomnia. When performing the same analysis as the primary analysis but excluding the hypersomnia item, it did not change the results. Furthermore, hypersomnia alone did not predict the treatment effect.

Discussion

This study's objectives were to investigate: (1) whether baseline SDS have a negative impact on treatment outcomes independent of treatment modality, and (2) whether SDS impact bCBT and TAU in routine care equally.

Overall, SDS did not have an impact on treatment response. However, when comparing the treatment arms, a difference was observed in the effect of SDS on treatment outcome between bCBT and TAU. Higher baseline SDS indicated a decreased treatment response in the bCBT group, while TAU was unaffected. Interestingly, the effect of baseline SDS was only present at 12-months follow-up. This finding points to a long-term effect of SDS on the course of depression following bCBT, even though treatment initially seems unaffected. Despite the effect being small, it was supported by the fact that SDS also significantly affected the risk of being diagnosed with MDD at 12-months follow-up in the bCBT group.

However, in a secondary analysis of a subgroup of sites we compared bCBT only with face-to-face CBT. This analysis showed that while SDS still significantly impacted bCBT, there was no significant difference between treatment-arms in this subgroup. Not surprisingly, this could indicate

that the face-to-face and blended CBT conditions were more similar in content and outcome compared with the remaining TAU formats. Perhaps the less structured TAU conditions were slightly more attentive to the presence of SDS, indicating a shortcoming in common CBT-protocols for MDD.

This study found results that support prior research but also results that contradict previous findings. In line with prior research and our hypothesis, bCBT was affected by SDS. However, contrary to this, TAU and the face-to-face CBT subgroup were unaffected by SDS.

The finding that SDS have a negative impact on bCBT represents an important addition to the existing literature on SDS and MDD treatment. It is in accordance with prior research showing an increased risk for MDD non-remission following FTF treatment [11,12,14], as well as studies showing that insomnia symptoms decrease treatment response in iCBT [23,24]. Hence, the present results extend the findings from prior research by confirming the association between SDS and treatment response for MDD in a new treatment format, bCBT.

Further, the analyses showed that a higher endorsement of sleep disturbance items at baseline was associated with a lower treatment response at 12-months follow-up. This corroborates the findings of Pigeon et al. [13] and Troxel et al. [14]. However, while these authors only used a dichotomous measure of MDD (remission vs. non-remission), the present analyses expanded this by showing an association between severity of SDS and the degree of symptom alleviation at 12-months follow-up.

While the long-term effect of baseline SDS on bCBT for MDD is in line with prior research [13], the present finding that treatment response at 3- and 6-months follow-up was unaffected by SDS is not. Different explanations may apply. First, none of the previous studies investigated bCBT. This finding may be uniquely associated with bCBT. However, there are no clear indications as to why this should be the case. Secondly, neither MDD nor SDS has been measured uniformly in previous research. Notably, the present study used sleep disturbance items from a depression scale (QIDS) to measure

SDS. While this method has been validated [37,43], it is not the most reliable measure of SDS. In the study by Troxel et al. [14], subjectively measured SDS did not predict treatment outcome alone, but it did when coupled with an objective indicator. Another notable difference is the outcome measures used across these studies. As mentioned, previous research has generally focused on dichotomous outcomes [12-14], whereas the present study used the PHQ-9 to measure the size of the treatment effect. If the MINI had been applied at 3- and 6-months follow-up as well in the present study, it would have been interesting to compare the dichotomous findings regarding non-remission at these time points. These differences might affect the comparability to the studies, and therefore the present findings should not discount prior research.

The missing effect of SDS on TAU is also noteworthy. It might indicate that TAU practitioners were more attentive to SDS and implemented an SDS intervention when necessary. However, this is still contrary to Pigeon et al. [13], who found a significant effect of insomnia on MDD treatment in routine care. Having said that, it may be worth noting that the study by Pigeon et al. [13] is relatively old. It could be hypothesized that due to the increased attention to SDS in the past years (e.g. [8,10]), routine care practitioners may treat patients reporting SDS differently today. This may help explain why TAU was unaffected by SDS in the present study. It is highly speculative, though.

Strengths and limitations

Some strengths of this study are worth noting. Primarily, this study used a randomized and longitudinal design with multiple measurement points. Using this design, we can determine how well bCBT compares to established effective treatments. Furthermore, we can determine how well treatment effects are sustained following treatment.

Secondly, this study utilized a large, heterogeneous sample, spanning nine different European countries lending the study great ecological validity. Further, the comparison between TAU and bCBT provides clinically useful results, as TAU reflects the everyday treatments delivered by

clinicians rather than the standardized treatments of a research trial. This part of the design could also be framed as a weakness since an efficacy study using only standardized protocols can be easier to interpret. However, this would have been at the cost of the finding's generalizability [44], which was highly important in the E-COMPARED study [31].

Some limitations for the present analyses should also be taken into account. Primarily, the E-COMPARED study was not geared to investigate a research question regarding SDS, which is highlighted by the lack of a dedicated insomnia measure. However, as indicated by Manber et al. [37], the items from the QIDS perform satisfactorily in discriminating the presence of SDS. Further, we decided to pool hypersomnia and insomnia items to establish an aggregated SDS score. Given the higher prevalence of insomnia, as was also evident in the present sample, this approach might be considered questionable. Focusing solely on insomnia symptoms would provide a clearer picture as to what SDS entails. However, given that hypersomnia and insomnia symptoms may co-occur and have been associated with more severe depression in adolescents [18,19], capturing the full phenomenon seemed prudent.

This study provides important findings regarding the use of bCBT to treat MDD with marked SDS. When the treatment format moves from face-to-face to internet-based, the potential for broader dissemination generally comes at the cost of treatment flexibility. The present analyses indicated that SDS might affect the less flexible treatment format, bCBT, more than it affects TAU. However, given that this was a secondary analysis of a study that was not designed to test this hypothesis, the results should be interpreted cautiously. It will be important for future research to test if these findings are supported when using dedicated sleep disturbance measures. Nonetheless, it would also be of interest to see if treatment outcomes in bCBT can be improved by using online add-on sessions for SDS. Prior research has shown that iCBT can effectively treat SDS (e.g. [25,45-48]), and there is a call for research on sequential or concomitant treatment of MDD and SDS [49]. Lastly, it is of interest to

investigate if these findings extend to other forms of diagnostic complexity. Future studies should compare bCBT with face-to-face therapy for MDD patients with other common comorbidities such as alcohol use or anxiety disorders.

Conclusion

Baseline SDS may have a negative impact on long-term treatment outcomes in bCBT for MDD. TAU seems to be unaffected by the severity of baseline SDS. This suggests that extra attention to comorbidity such as SDS, which was investigated here, might be important when treating depression with bCBT in routine care.

Future research should investigate, whether there is an improved treatment outcome in bCBT for MDD with comorbid SDS when using add-on modules targeting SDS.

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Conflicts of interest

None

Abbreviations

bCBT: Blended cognitive behavioral therapy
CBT: Cognitive behavioral therapy
E-COMPARED: The European COMPARative Effectiveness research on blended Depression treatment versus treatment-as-usual
FTF: Face-to-face
iCBT: Internet-based cognitive behavioral therapy
MDD: Major depressive disorder
MINI: Mini-international neuropsychiatric interview
PHQ-9: Patient health questionnaire-9
QIDS: Quick inventory for depressive symptomatology

RCT:	Randomized	controlled	trial
SDS:	Sleep	disturbance	symptoms
TAU:	Treatment	as	usual

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Supplementary Files

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Figures

Changes in symptoms severity of depression and SDS from baseline to 12-months follow-up. Abbreviations: bCBT = Blended cognitive behavioral therapy, dep. = depression, PHQ-9 = Patient health questionnaire-9, SDS = Sleep disturbance symptoms.