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7

The efficacy of cognitive behavioral therapy and psychodynamic therapy in the outpatient treatment of major depression: a randomized clinical trial

This chapter is submitted as:

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Abstract

Objective: The efficacy of psychodynamic therapies for depression remains open to debate due to a paucity of high-quality studies. We compared the efficacy of psychodynamic therapy to cognitive behavioral therapy (CBT), hypothesizing non-significant differences and the noninferiority of psychodynamic therapy to CBT.

Method: 341 Adults meeting DSM-IV criteria for a major depressive episode and with *Hamilton Depression Rating Scale* (HAM-D) scores ≥ 14 were randomized to 16 sessions of individual manualized CBT or short-term psychodynamic supportive therapy. Severely depressed patients (HAM-D >24) received additional antidepressant medication according to protocol. Post-treatment remission rates (HAM-D ≤ 7) constituted the primary outcome measure. Secondary outcome measures included mean post-treatment HAM-D and patient-rated depression scores and one-year follow-up outcomes. Data were analyzed with generalized estimating equations and mixed model analyses using intention-to-treat samples. Noninferiority margins were pre-specified as odd's ratio=0.49 for remission rates and Cohen's $d=0.30$ for continuous outcome measures.

Results: No statistically significant treatment differences were found for any of the outcome measures. The average post-treatment remission rate was 22.7%. Noninferiority was shown for post-treatment HAM-D and patient-rated depression scores, but could not be demonstrated for post-treatment remission rates or any of the follow-up measures.

Conclusions: Our findings extend the evidence-base of psychodynamic therapy for depression, but also show that time-limited treatment is insufficient for a substantial number of patients encountered in psychiatric outpatient clinics. These findings indicate the urgent need to improve psychotherapy outcomes and to consider the wisdom of the current press to limit treatment duration.

Trial registration: Current Controlled Trials ISRCTN31263312 (<http://www.controlled-trials.com>)

Introduction

Major depressive disorder is a highly prevalent mental disorder, substantially debilitating patients and carrying a tremendous financial burden to society (Kessler et al., 2003; World Health Organization, 2001). Patients seeking treatment for depression typically are offered antidepressant medication or psychotherapy alone or in combination (Marcus & Olfson, 2010). Given that antidepressants might not be as specifically efficacious as was previously believed (Fournier et al., 2010; Kirsch et al., 2008; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008), treatment guidelines increasingly advocate the option of psychotherapy for mild-to-moderate depression (American Psychiatric Association [APA], 2010; National Institute for Health and Clinical Excellence [NICE], 2009).

However, efficacy research with respect to psychotherapy for depression needs to be broadened in two ways. First, the efficacy of psychodynamic therapy remains controversial due to an absence of adequately conducted trials (APA, 2010; Driessen et al., 2010; Gerber et al., 2012; NICE, 2009). Second, while different psychotherapeutic approaches for depression are considered equally efficacious by many (Cuijpers, van Straten, Andersson, & van Oppen, 2008), high-quality studies directly comparing psychotherapies for depression are rare (Weissman, 2007) and the literature is dominated by superiority trials designed to show significant differences between conditions, which cannot demonstrate equal efficacy (Piaggio, Elbourne, Altman, Pocock, & Evans, 2006).

We report a randomized clinical trial comparing the efficacy of psychodynamic therapy with cognitive behavioral therapy (CBT) among patients seeking treatment for a major depressive episode in psychiatric outpatient clinics (Driessen et al., 2007). We first examined whether treatment outcomes differed significantly, and in case of non-significant differences, examined whether psychodynamic therapy was noninferior to CBT. We hypothesized no significant differences between the modalities and noninferiority of psychodynamic therapy to CBT at post-treatment and one-year follow-up.

161

Methods

Design

This study is a randomized clinical trial with a CBT:psychodynamic allocation ratio of 1:1. The Dutch Union of Medical-Ethic Trial Committees for mental health organizations approved the study design.

Participants

Participants were referred by their general practitioner to one of three psychiatric outpatient clinics in Amsterdam, The Netherlands. Inclusion criteria were: 1) presence of a major depressive episode according to DSM-IV criteria as assessed with the *MINI-International Neuropsychiatric Interview – Plus* (MINI-Plus; Sheehan et al., 1998), 2)

Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) scores ≥ 14 , 3) age 18-65 years, and 4) written informed consent after complete description of the study.

Exclusion criteria included presence of psychotic symptoms or bipolar disorder, severe suicidality warranting immediate intensive treatment or hospitalization, substance misuse/abuse in the last six months, pregnancy, inability to meet trial demands, and use of psychopharmacology or other medications that might influence mental functions. Patients using antidepressants were included only if the medication they were currently taking was judged to be inefficacious by both the patient and the intake psychiatrist. If so, the patient was tapered off the medication under medical supervision and baseline assessment took place after a washout period of at least one week after medication stopped ($n=25$, 16 of whom subsequently restarted medication during the study proper).

Interventions

Both psychotherapies encompassed 16 individual sessions within 22 weeks and were conducted according to published treatment manuals for the respective interventions (de Jonghe, 2005; Molenaar, Don, van den Bout, Sterk, & Dekker, 2009), both suitable for application to a broad group of patients, including those with non-North-West European cultural backgrounds. CBT was based on the principals of Beck (1976) and included behavioral activation and cognitive restructuring according to a session-by-session protocol with home-work assignments. Short-term psychodynamic supportive psychotherapy (de Jonghe, 2005, de Jonghe et al., in press; de Jonghe, Kool, van Aalst, Dekker, & Peen, 2001; de Jonghe et al., 2004; Dekker et al., 2005; Dekker et al., 2008) was used to represent the psychodynamic intervention. This modality involved an open patient-therapist dialogue that used supportive and insight-facilitating techniques to address the depression's emotional background by virtue of discussing current relationships, internalized past relationships and intrapersonal patterns.

Psychotherapists in both conditions were psychologists or psychiatrists with at least master- or MD-degree, who followed a three-day course in short-term psychodynamic supportive psychotherapy or a 100-hour basic CBT training accredited by the Dutch Association for Behavioral and Cognitive Therapy. Moreover, all therapists adequately conducted at least one intensively supervised therapy case in accordance with the relevant treatment manual as judged by a study supervisor. Although no formal assessments were conducted, manual adherence was checked by means of bi-weekly supervision sessions chaired by a study supervisor in which audiotaped material was discussed. All supervisors were registered supervisors with either the Dutch Association of Psychoanalytic Psychotherapy (one being in training) or the Dutch Association for Behavioral and Cognitive Therapy. Differences in the number of years that the supervisors had been conducting their respective modalities were minimal (CBT: 10.9, $SD=11.0$; psychodynamic: 9.7; $SD=2.9$), but somewhat larger with respect to years conducting supervision (CBT: 14.6, $SD=10.3$; psychodynamic: 6.3; $SD=3.2$), although neither difference was significant.

Thirty-seven CBT therapists and 56 psychodynamic therapists treated on average respectively 4.2 (range=1-16) and 3.0 (range=1-12) patients. No differences between

treatment conditions were found for average number of times a patient was discussed in supervision (CBT: 4.3, psychodynamic: 4.6) or the mean number of therapy sessions received (CBT: 10.6, psychodynamic: 10.9; mean numbers being lower than the maximum of 16 due to premature termination, drop-out and patients missing sessions). Regarding therapist protocol adherence, CBT therapists reported a mean score of 7.1 (scale=0-10) over 1218 CBT sessions. Conditions did not differ regarding therapists post-master/MD years of clinical experience (CBT: 7.5, SD=7.3; psychodynamic: 7.4, SD=6.7), but CBT more often was conducted by psychologists, while psychodynamic therapy more often was conducted by psychiatrists ($\chi^2(1)=109.80$, $p<.001$). Furthermore, CBT was conducted more often by a female therapist than was the case for psychodynamic therapy ($\chi^2(1)=15.91$, $p<.001$). We therefore conducted a sensitivity analysis controlling for therapist gender and profession.

Severely depressed patients (HAM-D>24 at baseline; $n=129$) and moderately depressed patients at baseline that developed severe symptoms during psychotherapy monotherapy ($n=21$) were offered additional antidepressant medication administered by a psychiatrist (who was not the patient's psychotherapist) according to a protocol starting with extended-release venlafaxine 75 mg/day that could be raised to a maximum of 225 mg/day. In case of intolerance or nonresponse, venlafaxine was switched to either citalopram or nortriptyline. Pharmacotherapy consults addressed symptom evaluation, side-effects and adherence. Three research psychiatrists supervised pharmacotherapy.

Eight patients (6.2%) did not start the recommended pharmacotherapy and 14 (10.8%) switched medication during treatment. The number of patients not starting pharmacotherapy, the pharmacotherapy doses used, and patient-reported medication adherence did not differ significantly between the treatment conditions.

Outcome measures

The primary outcome measure was post-treatment remission rate (HAM-D \leq 7). Secondary outcome measures included follow-up remission rates, and post-treatment and follow-up observer-rated (HAM-D; Hamilton, 1960) and patient-rated mean depression scores (*Inventory of Depressive Symptomatology, Self-Report*; Rush et al., 1996).

Trained research assistants (master-level graduate students in clinical psychology) assessed the HAM-D according to the Dutch scoring manual (de Jonghe, 1994). Assessors engaged in one-hour peer supervision sessions bi-weekly, in which audiotaped interviews were discussed. The average intraclass correlation coefficient over 46 audiotaped assessments scored by multiple assessors was .97. Both observer-rated and patient-rated depression measures showed good reliability at baseline assessment (Cronbach's $\alpha=.75$ and $.78$, respectively). HAM-D assessors were not blind to treatment condition. We therefore asked the assessors' hypotheses regarding treatment effects at post-treatment and follow-up and conducted a sensitivity analysis controlling for these variables.

Randomization

Separate random allocation sequences were generated for each of the three clinics by one of the authors (JP) using the SPSS random number generator. Randomization was stratified by gender and age (<32.5/>32.5). Research assistants, aware of the allocation sequence, enrolled participants and assigned them to interventions.

Statistical Methods

Analyses were based on an intention-to-treat sample, including all patients randomized. Patients were considered dropouts if they completed less than 8 psychotherapy sessions. Response was defined as a reduction of HAM-D scores $\geq 50\%$ at post-treatment.

Given the hierarchical data-structure, linear mixed model analyses were used for continuous outcomes, while logistic generalized estimating equations analyses were used for dichotomous outcomes. These analyses were preferred over logistic mixed model analyses due to the instability of the latter (Twisk, 2006). Examining pre- to post-treatment outcomes, we excluded follow-up data (in which additional help-seeking could not be controlled) from the analyses. Mixed model analyses were conducted according to a three-level structure (therapist, patient, repeated measures). Location was included as a covariate in a sensitivity analysis, rather than a level, because of the small number of categories ($n=3$). Mixed model analyses were performed with MLwiN (version 2.22). All other analyses were performed with SPSS (version 16.0).

164

We started with a basic model including main effects for treatment and time and a time-by-treatment interaction. Time was treated as a categorical variable, to assess treatment effects at the different time points. To control for possible confounds, we next added the following sets of covariates: 1) clinic, and number of patients with baseline HAM-D >24 , 2) demographic variables as reported in Table 1, 3) depression characteristics as reported in Table 1, 4) therapist profession and gender, 5) HAM-D assessors' treatment outcome hypotheses, and 6) help-seeking during the follow-up period (as reported in Table 4). The estimated main effects for treatment at different assessment points under these different models were reported as odd's ratios with 95% confidence intervals (95%CI) for remission rates and differences in means for continuous outcomes. For the latter, we also calculated effect sizes (Cohen's d) and 95%CI using Comprehensive Meta Analysis (version 2.2.046).

We then used a two-step strategy for the interpretation of outcomes. First, we examined whether treatment outcomes differed significantly. We considered treatment differences non-significant if the 95%CI included 1.00 or 0.00 for odd's ratios and effect sizes, respectively. This constituted our primary research question. Second, when differences were non-significant, we next examined whether psychodynamic therapy was noninferior to CBT by comparing outcomes to pre-specified noninferiority margins. These margins were determined based upon expert-opinion of 10 experienced depression research-clinicians (unaware of preliminary trial results) who rated a difference of 10% for remission rates and 2.6 for HAM-D scores (equivalent to Cohen's $d=0.30$) as the maximum difference allowable to conclude

noninferiority. Based on a maximum difference of 10% (12% and 22% remission rates) noninferiority margins for remission were set at odd's ratio=0.49. For all continuous outcome measures, noninferiority margins were pre-specified at $d=0.30$. We compared the 95%CI of the effect sizes and odd's ratios to the abovementioned pre-specified noninferiority margins and considered psychodynamic therapy noninferior to CBT on a given outcome measure if the 95%CI's limit did not exceed the pre-specified noninferiority margin for that measure. This constituted our secondary research question. We repeated the main analyses in the subgroup of moderately depressed patients (HAM-D \leq 24) receiving psychotherapy only and in the subgroup of severely depressed patients (HAM-D $>$ 24) receiving combined psychotherapy and pharmacotherapy in order to investigate whether pooling these subgroups might have obscured differential patterns of results.

Power-analysis

An a-priori power-analysis (Driessen et al., 2007) indicated that we required 300 participants ($\alpha=.05$, $1-\beta=.80$) to answer our primary research question. To detect the 10% difference in remission rates between conditions that constituted the noninferiority margin ($\alpha=.05$, $1-\beta=.80$), 344 participants were needed (SPSS SamplePower for equivalence studies, one-tailed). Power to detect an outcome difference of $d=0.30$ for continuous outcome measures was .87.

165

Results

Participants

Figure 1 represents the participant flow. From April 2006 to December 2009, 4866 patients were assessed for eligibility during a standard intake procedure; 570 (11.7%) were found potentially eligible and invited for baseline assessment. Of these patients, 229 (40.2%) did not meet inclusion criteria or were not willing to participate. Therefore, 341 patients were randomized (CBT: 164, psychodynamic: 177). Characteristics of the sample are presented in Table 1. No significant differences were found between the conditions.

No significant differences were found between conditions regarding proportions of patients not completing treatment (CBT: 31.1%, psychodynamic: 25.9%). The majority of dropouts were patients that did not show up at treatment appointments without specifying a reason (53.9%). Recruitment was stopped when the intended number of participants was reached. One-year follow-up assessments were conducted from April 2007 to January 2011.

Post-treatment outcomes

Based on observed data, 24.3% (27/111) of the patients in the CBT condition and 21.3% (26/122) in the psychodynamic therapy condition met the remission criterion at post-treatment. Observed response rates were 38.7% (43/111) for CBT and 36.9%

Table 1: Baseline characteristics of the study sample.

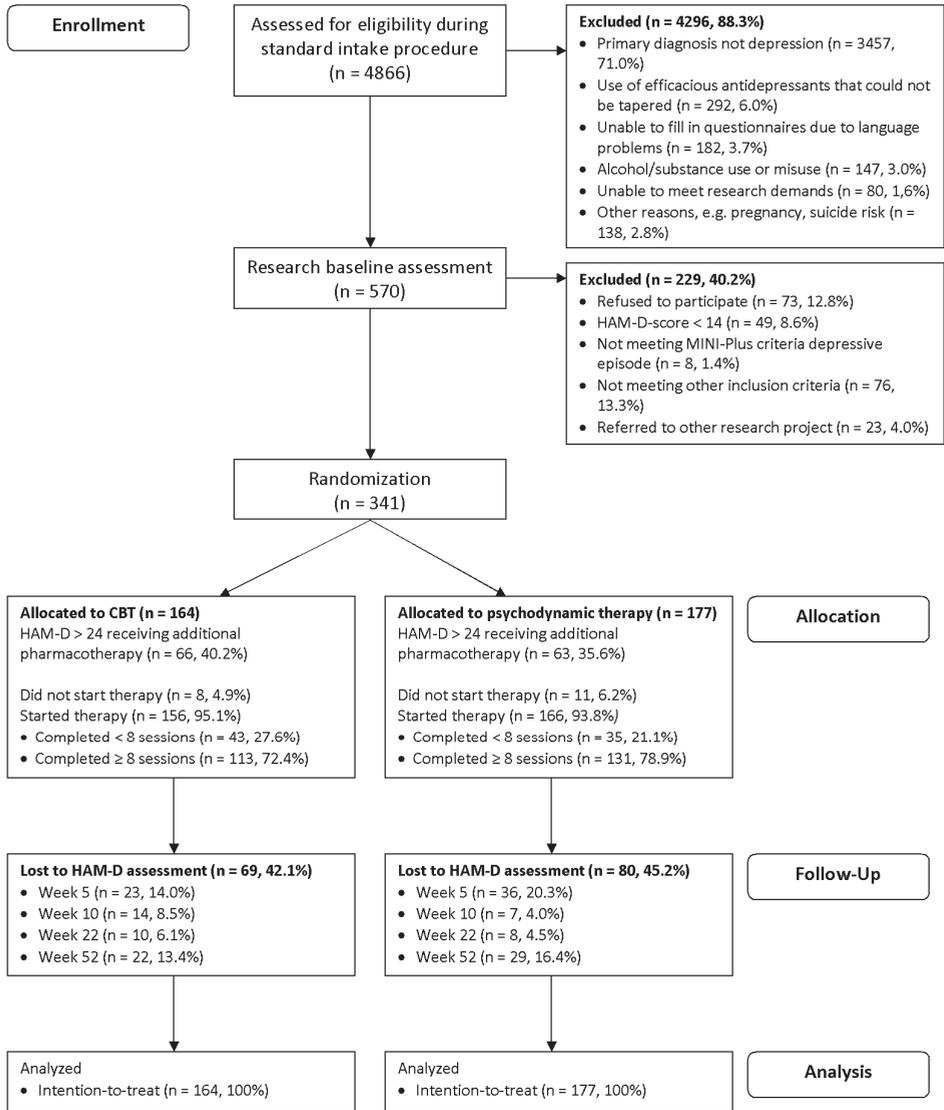
Variable	Total sample (n=341)	CBT (n=164)	Psychodynamic (n=177)	Test statistic (df)	p
Demographics					
Age (mean, SD)	38.91 10.30	38.27 10.13	39.49 10.44	t(339)=-1.09	.28
Gender (n, %)				$\chi^2(1)=0.21$.72
Male	102 29.9	51 31.1	51 28.8		
Female	239 70.1	113 68.9	126 71.2		
Cultural background (n, %)					
North-west European	186 55.0	92 56.1	94 54.0	$\chi^2(7)=6.71$.46
Other	152 44.9	72 43.9	80 46.0		
Marital status (n, %)					
Married	80 23.7	45 27.4	35 20.1	$\chi^2(4)=3.25$.54
Divorced	69 20.4	34 20.7	35 20.1		
Widowed	10 3.0	4 2.4	6 3.4		
Never married	176 52.1	80 48.8	96 55.2		
Other	3 0.9	1 0.6	2 1.1		
Living situation (n, %)					
Living with at least one other person	220 65.3	110 67.1	110 63.6	$\chi^2(2)=2.19$.35
Living alone	106 31.5	51 31.1	55 31.8		
Other	11 3.3	3 1.8	8 4.6		
Job status (n, %)					
Currently working	130 38.8	61 37.4	69 40.1	$\chi^2(5)=7.10$.22
Sickness benefits	55 16.4	35 21.5	20 11.6		
Social security benefits	74 22.1	34 20.9	40 23.3		
Disability benefits	32 9.6	13 8.0	19 11.0		
Student	14 4.2	5 3.1	9 5.2		
Other	30 9.0	15 9.2	15 8.7		
Educational level (n, %)					
Low	67 20.0	35 21.5	32 18.6	$\chi^2(3)=4.41$.22
Intermediate	159 47.5	71 43.6	88 51.2		
High	101 30.1	55 33.7	46 26.7		
Other	8 2.4	2 1.2	6 3.5		

Main income before taxes (n, %)							$\chi^2(1)=3.10$.08
	≤ €1273 a month	113	42.8	49	37.4	64	48.1	
	≥ €1274 a month	151	57.2	82	62.6	69	51.9	
Symptom severity								
	HAM-D score >24 (n, %)	129	37.8	66	40.2	63	35.6	$\chi^2(1)=0.78$
	HAM-D score (mean, SD)	23.40	5.35	23.68	5.47	23.14	5.24	t(339)=0.94
	Patient-rated depression score (mean, SD)	42.73	11.00	42.88	10.08	42.60	11.82	t(275)=0.21
	Comorbid Axis I disorder ^a (n, %)							$\chi^2(1)=0.00$
	No	204	59.8	98	59.8	106	59.9	
	Yes	137	40.2	66	40.2	71	40.1	
Depression characteristics								
	Duration present episode (n, %)							$\chi^2(4)=5.82$
	less than 6 months	84	25.1	48	29.8	36	20.8	
	6 months to 1 year	88	26.3	43	26.7	45	26.0	
	1 to 2 years	43	12.9	22	13.7	21	12.1	
	more than 2 years	86	25.7	35	21.7	51	29.5	
	unknown	33	9.9	13	8.1	20	11.6	
	Prior treatment for current depressive episode (n, %)							$\chi^2(1)=1.37$
	No	218	65.3	100	62.1	118	68.2	
	Yes	116	34.7	61	37.9	55	31.8	
	Number of prior depressive episodes (n, %)							$\chi^2(2)=2.23$
	None	103	31.1	55	34.6	48	27.9	
	One	69	20.8	29	18.2	40	23.3	
	Two or more	159	48.0	75	47.2	84	48.8	
	Comorbid dysthymia (n, %)							$\chi^2(1)=0.53$
	No	194	66.0	94	68.1	100	64.1	
	Yes	100	34.0	44	31.9	56	35.9	

^a Comorbid Axis I disorders were assessed by the psychotherapists during treatment without the use of a structured interview and comorbidity rates might therefore be underestimated.

CBT = cognitive behavioral therapy, HAM-D = Hamilton Depression Rating Scale, SD = standard deviation.

Figure 1: Flowchart of participants through the different research phases



168

Note: percentages might not add up due to rounding of numbers

CBT = cognitive behavioral therapy, HAM-D = Hamilton Depression Rating Scale, MINI-Plus = MINI International Neuropsychiatric Interview – Plus.

(45/122) for psychodynamic therapy. Estimated odd's ratios for remission at different assessment points are listed in Table 2. At post-treatment, the odd's ratio was 0.82 (95%CI:0.45-1.50), indicating that remission rates did not differ significantly. The 95%CI odd's ratio's lower limit exceeded the pre-specified noninferiority margin of 0.49. This pattern of results did not change when different sets of covariates were added (Table 2).

Mean observer-rated and patient-rated depression scores during treatment in both treatment conditions are presented in Figure 2, showing that depressive symptom scores in both conditions improve over time. Estimated observer-rated and patient-rated mean differences at different assessment moments are presented in Table 2, along with effect sizes of the post-treatment differences between conditions. At week 22, the estimated observer-rated difference between treatment conditions is 0.24 HAM-D points (SE=0.90) corresponding with an effect size of $d=0.02$ (95%CI:-0.24-0.27), indicating that treatment differences were non-significant. The estimated patient-rated difference between treatment conditions is 1.94 points (SE=1.92), corresponding with an effect size of $d=-0.08$ (95%CI:-0.38-0.22), also indicating differences were not significant. Both upper limits of the effect sizes 95%CIs did not exceed the pre-specified noninferiority margin of $d=0.30$. This pattern of results did not change when controlling for different covariates, although the noninferiority margin was slightly exceeded when controlling for number of patients with baseline HAM-D-scores>24 and clinic (HAM-D estimated mean difference=0.64, SE=0.81; $d=0.05$, 95%CI:-0.21-0.31).

In the moderately depressed subgroup, CBT and psychodynamic therapy observed remission rates were respectively 26.5% (18/68) and 27.7% (23/83), with estimated odd's ratios (1.02; 95%CI:0.50-2.06), observer-ratings ($d=-0.05$, 95%CI:-0.37-0.27), and patient-ratings ($d=-0.24$, 95%CI:-0.61-0.13) all indicating noninferiority of psychodynamic therapy to CBT. In the severely depressed subgroup receiving additional pharmacotherapy, CBT and psychodynamic therapy observed remission rates were respectively 20.9% (9/43) and 7.7% (3/39), with estimated odd's ratio (0.31; 95%CI:0.08-1.26), observer-ratings ($d=0.21$, 95%CI:-0.23-0.64), and patient-ratings ($d=0.17$, 95%CI:-0.35-0.69) all indicating no significant differences, without demonstrating noninferiority.

Follow-up outcomes

Follow-up assessments were conducted with 192 (56.3%) participants (Figure 1). As shown in Table 4, a non-significant trend ($\chi^2(1)=2.67$, $p=.10$) indicated that more patients reported additional treatment during the follow-up period in the CBT condition ($n=41$; 44.6%) than in the psychodynamic therapy condition ($n=32$; 33.0%).

Based on observed data, 34.7% (33/95) of the patients in the CBT condition and 26.8% (26/97) of the patients in psychodynamic therapy condition met the remission criterion. The estimated odd's ratio of remission rates at follow-up was 0.74 (95%CI:0.41-1.34; Table 3), indicating that remission rates did not differ significantly. The 95%CI odd's ratio's lower limit exceeded the pre-specified noninferiority margin of

Table 2: Treatment effects at the different assessment moments according to the basic model of analysis and when corrected for different sets of covariates.

Time and Model	Remission		Hamilton Depression Rating Scale			Inventory of Depressive Symptomatology					
	odd's ratio	95%CI	Estimated mean difference	Difference	SE	Effect size	Estimated mean difference	Difference	SE	Effect size	95%CI
Week 0											
Model 1				-0.55	0.78		-0.31	1.62			
Model 2				-0.21	0.69		0.35	1.51			
Model 3				-0.65	0.77		-0.40	1.55			
Model 4				-0.42	0.80		0.05	1.63			
Model 5				-0.88	0.95		-1.33	1.98			
Model 6				-0.56	0.79		-0.29	1.64			
Week 5											
Model 1	0.61	0.19-1.98	0.46	0.88							
Model 2	0.58	0.18-1.87	0.79	0.79							
Model 3	0.52	0.17-1.65	0.30	0.87							
Model 4	0.44	0.13-1.55	0.68	0.89							
Model 5	0.65	0.19-2.25	0.11	1.03							
Model 6	0.62	0.19-2.03	0.58	0.89							
Week 10											
Model 1	1.26	0.58-2.77	1.00	0.89			1.34	1.85			
Model 2	1.22	0.56-2.66	1.34	0.81			1.74	1.74			
Model 3	1.13	0.50-2.59	0.92	0.88			1.32	1.79			
Model 4	1.11	0.49-2.50	1.22	0.91			1.95	1.85			
Model 5	1.35	0.56-3.22	0.64	1.05			0.25	2.19			
Model 6	1.31	0.60-2.85	0.83	0.91			1.04	1.87			
Week 22											
Model 1	0.82	0.45-1.50	0.24	0.90		0.02	-0.24	0.27		1.92	-0.08
Model 2	0.78	0.42-1.43	0.64	0.81		0.05	-0.21	0.31		1.82	-0.07
Model 3	0.70	0.36-1.38	0.14	0.89		0.01	-0.25	0.27		1.88	-0.08
Model 4	0.72	0.38-1.35	0.36	0.91		0.03	-0.23	0.28		1.93	-0.08

Model 5	0.89	0.41-1.93	-0.12	1.05	-0.01	-0.26-0.25	-2.99	2.26	-0.10	-0.40-0.20
Model 6	0.83	0.45-1.53	0.31	0.91	0.02	-0.24-0.28	-1.96	1.94	-0.08	-0.38-0.23

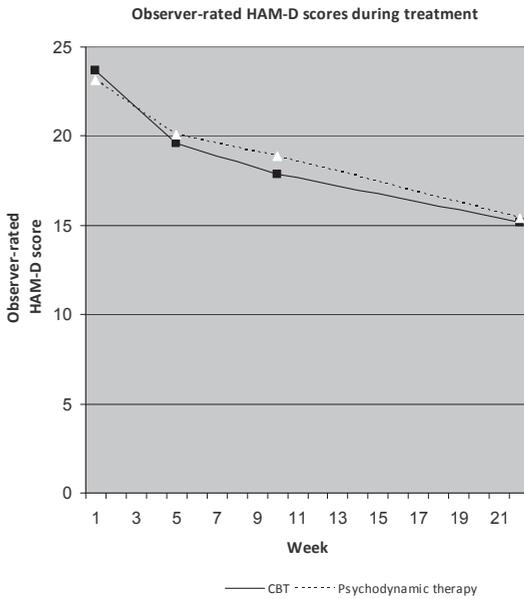
Note: Model 1: basic model including treatment, time and time*treatment interactions; Model 2: basic model with HAM-D>24 and clinic added as covariates
 Model 3: basic model with demographic variables (see Table 1) added as covariates; Model 4: basic model with clinical variables (see Table 1) added as covariates; Model 5: basic model with therapist gender and profession added as covariates; Model 6: basic model with HAM-D assessors' hypotheses regarding treatment outcomes added as covariates
 SE = standard error.

Table 3: Follow-up outcomes according to the basic model of analysis and when corrected for different sets of covariates.

Model	Remission		Hamilton Depression Rating Scale			Inventory of Depressive Symptomatology				
	odd's ratio	95%CI	Estimated mean difference		Effect size		Estimated mean difference		Effect size	
			Difference	SE	d	95%CI	Difference	SE	d	95%CI
Model 1	0.74	0.41-1.34	1.94	1.01	0.14	-0.14-0.42	2.99	2.22	0.12	-0.23-0.48
Model 2	0.69	0.38-1.27	2.36	0.93	0.18	-0.10-0.47	3.49	2.14	0.15	-0.21-0.51
Model 3	0.64	0.33-1.26	1.82	1.00	0.13	-0.15-0.42	3.37	2.17	0.14	-0.22-0.50
Model 4	0.61	0.33-1.14	2.20	1.02	0.16	-0.13-0.44	3.16	2.23	0.13	-0.23-0.49
Model 5	0.72	0.35-1.47	1.62	1.15	0.10	-0.18-0.38	1.94	2.52	0.07	-0.29-0.43
Model 6	0.75	0.41-1.37	1.95	1.02	0.14	-0.15-0.43	3.16	2.26	0.13	-0.23-0.49
Model 7	0.68	0.35-1.33	1.74	1.09	0.12	-0.17-0.41	2.68	2.31	0.11	-0.26-0.47

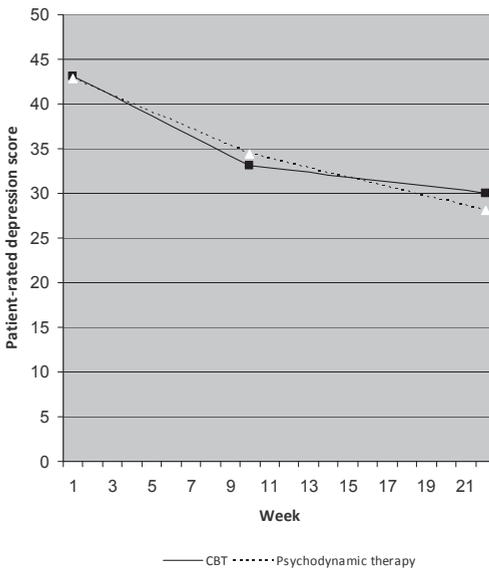
Note: Model 1: basic model including treatment, time and time*treatment interactions; Model 2: basic model with HAM-D>24 and clinic added as covariates;
 Model 3: basic model with demographic variables (see Table 1) added as covariates; Model 4: basic model with clinical variables (see Table 1) added as covariates; Model 5: basic model with therapist gender and profession added as covariates; Model 6: basic model with HAM-D assessors' hypotheses regarding treatment outcomes added as covariates; Model 7: basic model with patient reported treatments in follow-up period added as covariates.
 SE = standard error.

Figure 2: Observer-rated and patient-rated mean depression scores during treatment



172

Patient-rated Inventory of Depressive Symptomatology scores during treatment



CBT = cognitive behavioral therapy, HAM-D = Hamilton Depression Rating Scale.

0.49. This pattern of result did not change when different sets of covariates were added (Table 3).

Estimated observer-rated and patient-rated mean differences at follow-up and corresponding effect sizes are presented in Table 3. Differences between treatment conditions were 1.94 HAM-D points (SE=1.01; $d=0.14$, 95%CI:-0.24-0.42), and 2.99 for patient-ratings (SE=2.22; $d=0.12$, 95%CI:-0.23-0.48), both indicating that treatment differences were not significant. Both upper limits of the effect sizes' 95%CIs exceeded the pre-specified noninferiority margin of $d=0.30$. This pattern of results did not change when controlling for different covariates (Table 3).

In the moderately depressed subgroup, observed remission rates were 40.0% (22/55) in the CBT condition and 35.4% (23/65) in the psychodynamic therapy condition (odd's ratio=0.84; 95%CI:0.41-1.73; observer-rated $d=0.08$, 95%CI:-0.28-0.44, patient-rated $d=0.02$, 95%CI:-0.40-0.45). In the severely depressed subgroup receiving additional pharmacotherapy, CBT and psychodynamic therapy observed remission rates were respectively 27.5% (11/40) and 9.4% (3/32; odd's ratio=0.27, 95%CI:0.07-1.08, observer-rated $d=0.32$, 95%CI:-0.15-0.79, patient-rated $d=0.40$, 95%CI:-0.27-1.07). All these differences were non-significant, but noninferiority could not be demonstrated on any of them.

Table 4: Additional treatments during the follow-up period by condition*

Variable	CBT		PDT		Statistic (df)	p-value
Any treatment, n (%)	41	(44.6)	32	(33.0)	$\chi^2(1)=2.67$.10
Antidepressant medication, n (%)	9	(9.8)	9	(9.3)	$\chi^2(1)=0.01$.91
<i>Number of consults, mean (SD)</i>	4.7	(4.3)	3.6	(1.7)	$t(16)=0.72$.48
Out-patient psychotherapy, n (%)	32	(34.8)	24	(25.0)	$\chi^2(1)=2.15$.14
<i>Number of sessions, mean (SD)</i>	5.8	(3.0)	6.5	(10.2)	$t(54)=2.75$.73
<i>Type of therapist, n (%)</i>					$\chi^2(2)=5.36$.07
Psychiatrist/psychotherapist	3	(9.7)	8	(36.4)		
Psychologist	21	(67.7)	11	(50.0)		
Unknown	7	(22.6)	3	(13.6)		
Day treatment, n (%)	0	(0.0)	1	(1.0)	$\chi^2(1)=0.95$.99
<i>Number of days, mean (SD)</i>	-	-	4	-	-	-
Inpatient treatment, n (%)	2	(2.2)	0	(0.0)	$\chi^2(1)=2.16$.23
<i>Number of days, mean (SD)</i>	15.5	(10.6)	-	-	-	-
Other treatment, n (%)	8	(8.7)	4	(4.2)	$\chi^2(1)=1.61$.20
<i>Number of sessions, mean (SD)</i>	6.1	(8.0)	6.0	(3.5)	$t(10)=0.03$.98

*Pharmacotherapy continuation according to protocol in the severely depressed subsample was not considered here.

Note: CBT = cognitive behavioral therapy.

Table 5: Serious adverse events during treatment and follow-up by condition

Type of event	Treatment		Follow-up	
	CBT	PDT	CBT	PDT
Alcohol abuse during consultation	0	1	0	0
Addition treatment started for:				
Increase of depressive symptoms	4	1	2	2
Suicidal ideation	2	4	1	1
Post-traumatic stress disorder	1	0	0	0
Pain symptoms	0	2	0	0
Psychosis	1	0	0	1
Severe antidepressant side effects	1	1	0	0
Major life event	1	2	0	0
Total (n)	10	11	3	4
Total (%)	6.1	6.2	1.8	2.3

Note: CBT = cognitive behavioral therapy ($n=164$); PDT = psychodynamic therapy ($n=177$)

Harms

174

Serious adverse events during treatment and follow-up are listed in Table 5 and mostly constituted an increase of depressive symptoms or suicidality for which additional treatment was needed. No differences were found between the conditions with regard to the proportion of patients reporting serious adverse events during treatment (CBT: 6.1%, psychodynamic: 6.2%) or follow-up (CBT: 1.8%, psychodynamic: 2.3%).

Discussion

Findings

We compared the efficacy of CBT and psychodynamic therapy for major depression in a large sample of patients treated in psychiatric outpatient clinics applying a randomized clinical design and noninferiority margins. Primary analyses indicated no significant differences between treatments at post-treatment. In secondary analyses, noninferiority could not be demonstrated for post-treatment remission rates, but was shown for post-treatment patient-rated and observer-rated depression scores. Follow-up findings again showed no significant differences between treatments, but noninferiority could not be demonstrated for any of the three outcome measures. However, the follow-up findings must be interpreted with caution, because of a non-significant trend suggesting that patients in the CBT condition received more additional treatment during the follow-up period. Our findings are in line with previous meta-analyses (Cuijpers et al., 2008; Driessen et al., 2010; Leichsenring, 2001) that reported no significant differences between individual CBT and psychodynamic therapy at post-treatment.

Post-hoc analyses revealed no significant differences between treatment conditions in the subgroup of moderately depressed patients receiving psychotherapy only and non-inferiority of psychodynamic therapy to CBT was shown on all post-treatment outcome measures in this group of patients. These findings add to the evidence-base of psychodynamic therapy for depression. No significant differences between treatments also were found in the subgroup of severely depressed patients receiving combined treatment, but differences were large enough to be significant if replicated in a larger sample, and non-inferiority could not be concluded in this group.

One notable finding of our study was that only 22.7% of the patients achieved remission at post-treatment, with 40% seeking additional treatment afterwards. These remission rates are lower than found in previous trials examining either short-term psychodynamic supportive psychotherapy (de Jonghe et al., 2004) or CBT (Dimidjian et al., 2006; Elkin et al., 1989). This might be related to this sample's relatively low socioeconomic status and income levels, which in naturalistic studies have been identified as predictors for less favorable treatment response (Löwe, Schenkel, Bair, & Göbel, 2005; Ostler et al., 2001), or to the relatively high rate of comorbid Axis I disorders. Our findings indicate that a substantial proportion of patients in specialized second-line outpatient clinics require more than time-limited treatment to achieve remission. These results are in line with findings regarding psychotherapy in 'real world' clinical practice (Morrison, Bradley, & Westen, 2003), and show that depression, as it is encountered in secondary care, can be characterized as a difficult-to-treat disorder. As residual depressive symptoms have been found to be the main predictor of future relapse (Paykel, 1998), this study's findings also indicate that psychotherapeutic treatment needs to be improved. For the present, our findings suggest that clinicians and policy makers ought to be modest about the expected outcome of time-limited depression treatments and that third party payers mandated limits on treatment duration that may lead to undertreatment of depression.

175

Strengths and limitations

This study has a number of strengths. First, a number of aspects add to the generalizability of this study's findings. Treatment was provided in regular psychiatric outpatient clinics by a large number of therapists with different experience levels. Patients were not recruited by advertisement, but instead were referred by general practitioners and no selection criteria with regard to previous treatment or suitability for psychotherapy were applied. Patients with relatively low socioeconomic statuses were included and almost half of the patient sample reported a non-North-West European (immigrant) cultural background. Second, we included severely depressed patients, which were additionally treated with pharmacotherapy prescribed according to a protocol. Third, this is the largest RCT comparing CBT and psychodynamic in the treatment of depression to date ($n=341$). By comparison, a total of 421 patients were included across 6 CBT-psychodynamic RCTs in a psychodynamic therapy for depression meta-analysis (Driessen et al., 2010). Finally, this was the first study to test whether psychodynamic therapy can be said to be noninferior CBT in the treatment of depression.

This study also has a number of limitations. First, we encountered a substantial number of patients that did not complete treatment or were lost to assessment. Mixed model analyses are robust with regard to missing data, but nevertheless a considerable portion of the patients missed out on the benefits of treatment. Second, treatment adherence was not systematically assessed, but was instead checked by means of intensive supervision by experienced supervisors and subjective therapist ratings. These ratings did suggest adequate adherence to the CBT manual, but no such measure of adherence was available with respect to psychodynamic treatment. Third, HAM-D assessors were not blind to treatment condition, therefore we cannot rule out observer bias. However, controlling for assessor-rated treatment expectations did not alter the pattern of results and results were similar for observer-rated and patient-rated outcomes. Fourth, research assistants enrolling participants were aware of the allocation sequence, which might have introduced selection bias. However, no significant differences were found with regard to any of the sample baseline characteristics. Fifth, although noninferiority margins were carefully thought through and based on clinical expert opinion, they were still set in an arbitrary fashion. Sixth, we could not prevent patients from seeking additional treatment during the follow-up period and a nonsignificant trend suggested that CBT patients may have returned to treatment more than patients in dynamic therapy. However, controlling for additional treatment in the follow-up period did not change the general pattern of results. Seventh, no control condition was included in this study.

176

Conclusion

No statistically significant differences were found between psychodynamic therapy and CBT in a large sample of patients treated for major depressive episode, with less than one-fourth of the patients reaching remission within 22 weeks of treatment. Noninferiority of psychodynamic therapy to CBT was shown for post-treatment mean depression scores, but could not be demonstrated for remission rates and follow-up measures. Our findings extend the evidence-base of psychodynamic therapy for depression, but also show that time-limited psychotherapy is not sufficient for a substantial number of patients encountered in psychiatric outpatient clinics. This suggests that there is an urgent need to improve psychotherapy outcomes and for policy makers to be aware of the possible negative effects of efforts to limit treatment duration.

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