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The Effectiveness of Cognitive Behavioral Analysis System of Psychotherapy for Chronic Depression: A Multisite Randomized Controlled Trial

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Abstract

Background:
Existing research into the treatment of chronic depression has mostly been conducted in academic settings. These situations do not represent regular care in mental health organizations. Pragmatic-applied research conducted in regular mental health care is therefore required to evaluate the feasibility and effectiveness of these treatments in the real-world, outpatient setting. The current study examined the feasibility and effectiveness of Cognitive Behavioral Analysis System of Psychotherapy (CBASP), a psychotherapy model developed specifically to treat chronic depression in 3 mental health care organizations in the Netherlands.

Method:
A randomized controlled trial was conducted comparing CBASP (n=69) with Care As Usual (CAU; n=73). Patients (aged 18-65) had a main diagnosis of chronic depression according to DSM-IV. CBASP consisted of a mean of 24 sessions conducted over one year. CAU consisted of a mean of 23 sessions of evidence-based treatments (e.g. Cognitive Behavioral Therapy, Interpersonal Psychotherapy, and Short term Psychoanalytic Supportive Psychotherapy) conducted over one year. Pharmacotherapy was provided in both arms. The Inventory for Depressive Symptomatology-Self-report (IDS-SR) was used as the primary outcome measure. The IDS was administered at pre-treatment, after 8, 16, 32, and 52 weeks. Patients with a 50% symptom reduction on the IDS were considered responders. Remission was defined as an IDS score of 13 or less.

Results:
Mean IDS scores dropped from 40.9 to 23.1 in the CBASP group and from 43.7 to 33.2 in the CAU group at week 52. There was no significant main effect between the two groups on the IDS (t = –1.10, P = .27), however, there was a significant treatment X time interaction (t =.-2.51, P = .01); patients assigned to CBASP had a greater reduction of depressive symptoms towards the end of the trial compared to patients assigned to CAU. Moreover, CBASP completers were more likely to respond (CBASP: 45.8% versus CAU: 15.4%, P =.001) and to remit (CBASP: 27.1% versus CAU: 7.7%, P =.01) and less likely to fulfill DSM-IV criteria for major depression compared to CAU completers (CBASP: 25.5% versus CAU: 65.3%, P <.001) at week 52.

Conclusion:
This trial shows that CBASP is, in the long run, more effective than standard evidence based treatments for chronic depression. The results are important as this is the first time that CBASP was tested rigorously in severe chronically depressed patients who had been referred to mental health care organizations, and against a high standard control condition.

Introduction

Major depressive disorder (MDD) frequently has a chronic course, with protracted episodes or incomplete remission between episodes.[1] Chronicity of depression is associated with increased comorbidity, greater service use, higher rates of suicidality, and poorer psychosocial functioning.[2,3] It is widely agreed that chronic depression is more difficult to treat than episodic major depression, and knowledge about optimal treatment approaches is emerging.[4]

Randomized, placebo-controlled trials have indicated that pharmacotherapy is efficacious in treating chronic depression.[4,5] A smaller, but growing, amount of randomized controlled trials have investigated the efficacy of psychotherapy for chronic depression.[2] In a meta-analysis of 17 studies it was found that psychotherapy had a small but significant effect (d=0.25) on chronic depression when compared to control groups, however, it was less effective in direct comparisons with pharmacotherapy (d=-0.31). The combination of both psychotherapy and pharmacotherapy was found to be more effective in comparisons with pharmacotherapy alone (d=0.23) and even more so in respect to psychotherapy alone (d=0.45).[6]

However, relatively positive effects were found for the Cognitive Behavioral Analysis System of Psychotherapy (CBASP), a psychotherapy developed specifically to treat chronic depression.[7] In a large randomized trial by Keller et al.[8] (n=681), CBASP was compared to the antidepressant Nefazodone, and to their combination. CBASP alone was equally effective when compared to Nefazodone alone (48% response rate), while the combination of both treatments was clearly superior (73% response rate). Moreover, CBASP was also effective as a maintenance treatment for chronic depression[9] and was found to be a good alternative for patients who were not motivated for or refractory to pharmacotherapy.[10]

The efficacy of CBASP was, however, not proved in a recent study by Kocsis et al.[11] In this study, chronically depressed patients were administered a 12 weeks trial of pharmacotherapy alone after which the nonresponder and partial-responder groups were augmented with either 12 weeks of CBASP or Brief Supported Psychotherapy (BSP). No differences between the augmented groups were obtained in the second study; in addition, no differences were found when the 2 augmentation groups were compared to a pharmacotherapy alone group.[11]

An explanation for these contradicting findings might be that the chronically depressed patients in the study by Kocsis et al.[11] were principally selected for a pharmacotherapy trial and therefore might have been more interested in pharmacotherapy and less motivated for psychotherapy. Furthermore, the patients in this study received less CBASP therapy sessions compared to the patients in the study by Keller et al.[8] (a mean number of 12.5 sessions versus

16.0 sessions). Finally, a longitudinal assessment of therapeutic response over time is still ongoing to determine whether the combination of CBASP plus medication and/or the combination of BSP plus medication might have long term benefits that were not apparent in the short run.[11]

Beside the mixed results obtained for CBASP, study results have been restricted to the assessment of efficacy.[6,12] These studies take place in academic settings, apply strict inclusion criteria, and participants are often recruited using advertisements in newspapers. These situations do not represent regular care in mental health organizations, where most chronically depressed patients have been in treatment for years, suffer severe symptomatology, report comorbid psychopathology, experience poor psychosocial functioning, and demonstrate a history of poor treatment response. Pragmatic-applied research, the methodology described below, is needed to evaluate the feasibility and effectiveness of treatment for chronic depression in the real-world, outpatient setting.

Testing the feasibility of a pragmatic-applied approach, the current study investigated the effectiveness of CBASP for chronic depression in 3 mental health care organizations in the Netherlands. CBASP was compared to Care As Usual (CAU), which consisted of evidence-based treatments such as Cognitive Behavioral Therapy (CBT),[13] Interpersonal Psychotherapy (IPT),[14] and Short Psychoanalytic Supportive Psychotherapy (SPSP).[15] Pharmacotherapy was provided in both arms. It was hypothesized that CBASP would produce a greater reduction in depressive symptoms than CAU, since CBASP has been specifically designed to treat chronic depression and has shown substantive results with this population in the past. [8-10]

Methods

Design

The present study, conducted between 2006 and 2010, is a two-armed multisite randomized controlled trial in which CBASP was tested against CAU over 52 week follow-ups. The study protocol is described in more detail elsewhere.[16] Patients were recruited within the Mood Disorder Departments of 3 sites (organizations for mental health care) in the Netherlands. Some patients were referred from inpatient units or emergency rooms, but all were treated as outpatients. They were approached by the research-coordinator and asked to participate in the study. The coordinator screened the patients with respect to the inclusion-exclusion criteria. If patients were willing and eligible to participate, written informed consent was obtained. After signing the informed consent form, patients were enrolled in the study and began with the baseline interview. After completing the baseline interview, patients were assigned at random to either CBASP or CAU. Randomization was performed by an external researcher using a computerized random number generator. Randomization was stratified per site. The same medication regimes were administered throughout the study for both CBASP and CAU. The design and conduct of the study were approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands.

Subjects

Patients (aged 18-65) were eligible to participate if their main diagnosis was a chronic form of depression according to the DSM-IV criteria:[17] a) a chronic major depressive disorder (i.e. existing for longer than 2 years) or b) a major depressive disorder superimposed on a dysthymic disorder or c) a recurrent major depressive disorder which, in the past 2 years, never fully remitted between episodes. The Mini International Neuropsychiatric Interview plus (M.I.N.I. plus) was used to assess chronic depression.[18] In addition, the level of symptom severity had to be moderate to severe, expressed as a score of 22 or more on the 28-item Inventory for Depressive Symptomatology (IDS-SR).[19] Patients were excluded from the study if they suffered from one (or more) of the following disorders: a psychotic disorder, bipolar disorder, organic brain syndrome, active substance abuse/dependence, severe borderline, schizotypical, or antisocial personality disorders. Patients were also excluded if there was an acute suicidal risk and if participants did not have a sufficient command of the Dutch language necessary to participate in the study.

Cognitive Behavioral Analysis System of Psychotherapy

CBASP is a psychotherapy model designed specifically to treat the pathological characteristics of the chronically depressed patients, such as extreme interpersonal fear and avoidance and an external locus of control, [20] which often stem from a developmental history filled with psychological insults and trauma.[21] In CBASP, besides the regular behavioral, cognitive and interpersonal techniques, specific techniques are used to replace the interpersonal fear of the chronic patient with interpersonal safety, starting within the therapeutic relationship. Subsequently, the relationship with the therapist is used as a tool to help patients to become more aware of their impact on others and to distinguish between adaptive and maladaptive relationships.[7] Comprehensive descriptions of CBASP and therapist and patient manuals have been published. [22-24]

In the current study, CBASP consisted of a mean of 24 sessions delivered over a period of a year. CBASP started with bi-weekly sessions in the first 4 weeks, followed, in principle, by 1 session per week from week 5-16. After 16 weeks (20 sessions), the session frequency was reduced to once every 2 weeks, followed by monthly sessions of CBASP up to week 52.

Before the beginning of this study, therapists were trained in CBASP during a 4 day workshop in which the basic techniques of CBASP were taught by James McCullough, Jr. Subsequently, 5 therapists were supervised by McCullough until they had received administration criteria. They then trained and supervised the participating study

psychotherapists. All therapists then treated 2 chronically depressed patients with CBASP under intense supervision before treating actual patients in the study. After 2 years, all therapists participated in another 4 day workshop by McCullough, to refresh and refine their skills. During the study, therapy sessions were audio taped, and the integrity of the therapists' adherence to protocol and performance was monitored by the site supervisors who used the audiotapes in supervision.

Care as usual

At the 3 sites, CAU consisted of evidence-based psychotherapies, such as CBT, IPT, or SPSP. Other interventions that were part of the treatment offered for chronically depressed patients were supportive or structured activities, and treatments that focused on relaxation, assertiveness, running, or other tasks. The treatment package received by patients in the CAU condition was registered throughout the study.

Pharmacotherapy

In both psychotherapy arms pharmacotherapy was provided. Pharmacotherapy consisted of guideline-driven antidepressant medication[25] and was supported by 'clinical management'.[26] Clinical management consisted of brief sessions in which patients were informed about the importance of adherence and the effects and side effects of medication. The use of medication (name, dose given, and blood levels if available) was registered for all patients throughout the study. Patients who refused to use medication were not excluded from the study, because CBASP has also been found to be effective as a monotherapy for chronically depressed patients.[8]

Outcome measures

The 28-item self-report version of the IDS[19] was used as the primary outcome measure. The IDS was administered at pre-treatment, mid-treatment (week 8), post-treatment (week 16), follow-up I (week 32), and at the end of the study, follow-up II (week 52). Patients with a 50% symptom reduction on the IDS, were considered responders. Remission was defined as an IDS score of 13 or less.[8,16] To assess chronic depression and comorbid disorders at baseline and at the end of the study patients received a diagnostic interview using the M.I.N.I. plus.[18]

Covariates

Information on demographic factors (age, gender, education, marital and employment status), age of onset of depression, and previous mental health treatment was collected at baseline. Childhood trauma was assessed retrospectively using the childhood trauma interview as used in the Netherlands Mental Health Survey and Incidence Study.[27] The assessments were performed by an experienced research nursing staff, who was not in the conduct of any of the interventions.

Data analysis

The randomized treatment groups were compared on baseline demographic and clinical variables. Analysis of variance (ANOVA) for continuous variables and χ^2 likelihood ratio statistics for categorical variables were employed. Similar analyses were used to compare dropouts and completers on baseline demographic and clinical variables.

Mixed-effects models based on maximum likelihood estimation were used to test treatment effectiveness because they are can account for different observations per patient. Furthermore, this modeling procedure can account for the changing symptomatic state of patients over the course of the trial. Mixed-effects linear regression analysis was used to compare the changes on the IDS scores between CBASP versus CAU. The model included a random intercept and fixed effects for treatment, site, time and the following covariates: age, sex, employment status, and age of onset of depression. Logistic regression analyses were used to compare treatment groups on the dichotomous outcome measures response, remission and the presence of a DSM-IV diagnosis of MDD at follow-up II. Covariates were included in the models based on baseline differences ($P \leq .15$) between the two groups (i.e. sex, age, employment status, age of onset of depression, and severity of depressive symptoms).

We imputed the missing values of age of onset of depression (8% missing values) by multiple imputations using the Imputation by Chained Equations module (ICE).[28] Next to the variable age of onset of depression, the imputation model comprised gender, age, employment status, and the IDS scores for all measurements. Fifty imputed data sets were used to reduce sampling variability from the imputation process.

Analyses were run on the completer's data set, in which we only imputed the variable age of onset of depression, as well as on the multiple imputed intention to treat data set, in which we also imputed the IDS scores for all measurements. Since the results from these data sets did not differ much from each other, we decided to report the results of the completers data set only.

Results

Subjects

A total of 213 patients were screened for the study (Figure 1). Of the 71 who were not eligible, 27 (38%) refused to participate, 19 (27%) the primary diagnosis was not chronic depression, 20 (28%) did not meet the study criteria, 1 (1%) had no insurance, and for 4 (6%) subjects the reason for non-participation was not known. A total of 142 patients underwent randomization: 69 were assigned to receive CBASP, and 73 to receive CAU.

Table 1 presents baseline sample demographic and clinical characteristics of these patients. There were no statistically significant differences between the two treatment groups. Of the total sample, only 22.7% was married (or cohabiting), and 42.3% was unemployed at study entry. The mean age of onset of depression was 24.5 years old (SD 13.2), and 82.0% had a history of mental health treatment in secondary or tertiary care.

Figure 1: flow chart

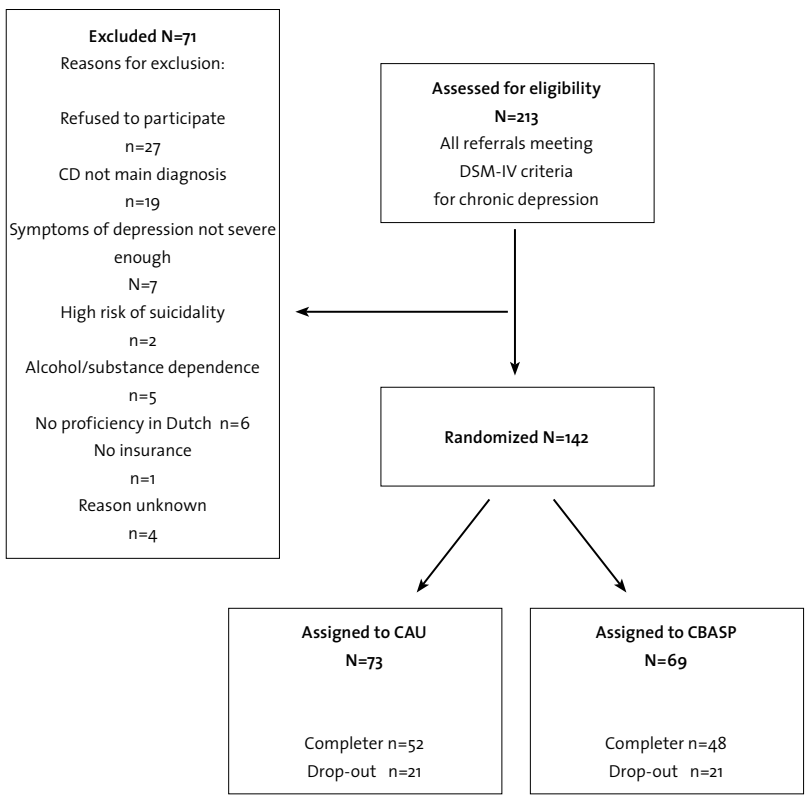

Table 1. Demographic, Social and Clinical Characteristics for the CAU group and the CBASP group

	CAU (n=73)	CBASP (n=69)	*P* [a]
Female (%)	49.4	63.9	.08
Age, mean ± SD, y	43.4 (10.0)	40.8 (11.2)	.14
Education mean ± SD, y	12.4 (3.6)	12.2 (3.2)	.65
Married or cohabiting (%)	23.6	21.7	.28
Employment status (%)			.09
Full time paid work (>32h)	27.4	31.9	
Part time paid work (3 to 32h)	21.9	34.8	
Unemployed / Seeking work / Registered sick / Disabled / Retired	50.7	33.3	
Age of onset, mean ± SD, y	26.5 (13.8)	22.4 (12.3)	.08
Antidepressant medication use (%)	58.9	69.7	.19
Previous mental health treatment (%) (secondary or tertiary care)	83.3	80.6	.68
Severity depressive symptoms (IDS score: 0-84), mean ± SD	43.7 (10.5)	40.9 (10.0)	.11
Comorbid anxiety disorder (current) (%)	57.4	58.2	.85
Childhood trauma (before age 16) (%)	69.9	68.1	.82

[a] Comparison between the CBASP and CAU group, using χ^2 likelihood ratio statistics (categorical variables) and ANOVA analyses (continuous variables).
Abbreviations: IDS = Inventory of Depressive Symptomatology.

At study entry patients had on average a severe level of depression severity, with a mean IDS score of 42.0 (SD 10.3). In addition, 58.2% also met DSM-IV criteria of one or more anxiety disorders (social phobia, panic disorder with or without agoraphobia, obsessive compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder), and 69% reported experiences of childhood trauma (e.g. emotional neglect, psychological abuse, physical abuse, sexual abuse).

Treatment delivery and drop-out

Patients assigned to CBASP attended a mean of 23.8 (SD = 11.4) therapy sessions, and patients assigned to CAU attended a mean of 22.8 (SD =13.7) therapy sessions (*P* = .64) (Table 2). Of the entire sample 64% used antidepressant medication during the study (69.7% in the CBASP group versus 58.9% in the CAU group; *P* = .19) (Table 1).

In total, 42 patients (30%) were lost to follow-up, 21 patients in the CBASP group and

21 patients in the CAU group (Figure 1). There were no significant differences on baseline demographic and clinical variables between the completers and noncompleters of the study.

Treatment outcomes

Mean IDS scores dropped from 40.9 to 23.1 in the CBASP group and from 43.7 to 33.2 in the CAU group at week 52 (Table 2). Mixed-effects linear regression analysis conducted on the IDS showed no significant main effect of CBASP versus CAU (t = –1.10, *P* = .27). However, there was a significant treatment X time interactions on the IDS (t = -2.51, *P* = .01), indicating that patients assigned to CBASP were more likely to have a greater reduction of severity of depressive symptoms in the last phase of the trial than patients assigned to CAU (Figure 2). In addition, patients who completed CBASP were more likely to respond (CBASP; 45.8% versus CAU; 15.4%, t = 3.20, *P* = .001), and to remit (CBASP; 27.1% versus CAU; 7.7%, t = 2.49, *P* = .01). Moreover, they were less likely to fulfill DSM-IV criteria for major depression compared to the patients who completed CAU (CBASP: 25.5% versus CAU: 65.3%, t = -3.67, *P* <.001) at follow-up II (week 52) (Table 3).

Table 2. Outcomes of CBASP versus CAU for Chronic Depression

	CBASP				
	Pre-treatment phase (week 0)	Mid-treatment phase (week 8)	Post-treatment phase (week 16)	Follow-up I continuation phase (week 32)	Follow-up II maintenance phase (week 52)
Cumulative number of sessions, mean (SD) (N)	NA	11.1 (3.8) (n=68)	16.8 (6.2) (n=68)	20.5 (8.8) (n=68)	23.8 (12.6) (n=68)
IDS scores, mean (SD) (N)	40.9 (10.0) (n=69)	33.9 (12.8) (n=55)	30.5 (14.2) (n=54)	28.3 (14.3) (n=49)	23.1 (13.6) (n=48)
	CAU				
Cumulative number of Sessions, mean (SD) (N)	NA	8.4 (5.4) (n=73)	13.6 (7.8) (n=73)	18.2 (10.9) (n=73)	22.8 (13.7) (n=73)
IDS scores, mean (SD) (N)	43.7 (10.5) (n=73)	36.3 (15.2) (n=61)	33.6 (16.2) (n=57)	31.1 (14.8) (n=43)	33.2 (13.9) (n=52)

Abbreviations: NA = not applicable; IDS = Inventory of Depressive Symptomatology.

Figure 2. Changes on IDS scores for CBASP versus CAU from pre-treatment (week 0) up until follow-II (week 52)

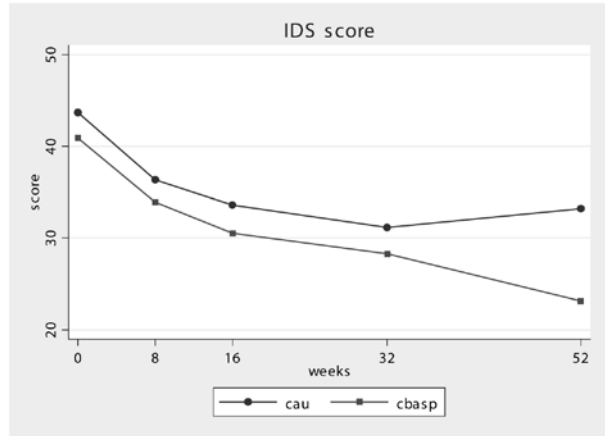

Table 3.Clinically Significant Changes of CBASP versus CAU for Chronic Depression Measured with IDS and MINI plus at Follow-up II (week 52)

	CBASP	CAU	t[c]	P[c]
Response[a] Nr (%)	22 (45.8) (n=48)	8 (15.4) (n=52)	3.20	.001
Remission[b] Nr (%)	13 (27.1) (n=48)	4 (7.7) (n=52)	2.49	.01
DSM-IV MDD diagnosis Nr (%)	12 (25.5) (n=47)	32 (65.3) (n=49)	-3.67	<.001

[a] Response is defined as a 50% symptom reduction on the IDS.

[b] Remission was defined as an IDS score of 13 or less.

[c] Using logistic regression analyses, adjusting for age, sex, employment status, severity of depressive symptoms (using the ISD) on baseline, and age of onset of depression.

Abbreviations: IDS, Inventory of Depressive Symptomatology; MINI plus, Mini International Neuropsychiatric Interview plus, Nr = Number.

Discussion

By applying a pragmatic approach, the present study sought to expand the methodologies used in studying chronic depression and extend the knowledge we have on the treatment of chronic depression. Building on earlier work investigating the efficacy of CBASP; the

current study investigated the feasibility and effectiveness of CBASP in 3 mental health care organizations in the Netherlands. CBASP was compared to Care As Usual (CAU), which consisted of evidence-based treatments such as CBT, IPT, and SPSP. As hypothesized, CBASP produced a greater reduction in depressive symptoms than CAU. In addition, rates of response (CBASP: 45.8% versus CAU: 15.4%) and remission (CBASP: 27.1% versus CAU: 7.7%) were significantly higher for patients treated with CBASP compared to those treated with CAU. Moreover, 74.5% of the patients who completed CBASP no longer met DSM-IV criteria for MDD, compared to 34.7% of the patients who completed CAU at 52 weeks follow-up.

It is important to note that the added effect of CBASP over CAU only became evident after the acute treatment phase ended suggesting that the added effects of CBASP over the other 3 commonly used treatments for depression took time to emerge. This could be due to its explicit focus on the pathological characteristics of chronically depressed patients, such as extreme interpersonal fear and avoidance, as revealed in their developmental history often filled with trauma (69% of our sample reported experiences of childhood trauma).[21] Since chronic patients, more often than not, disclose a lifelong history of interpersonal fear and avoidance, changing these chronic functioning patterns takes time.[7,29]

The finding that patients treated with CBASP kept improving during the maintenance phase of treatment has been reported before by Klein and colleagues.[9] It is therefore tempting to speculate that acute phase CBASP has long-term effects that persist when treatment sessions become less frequent or when they are stopped altogether. This might also explain why Kocsis et al.[11] did not find that CBASP in combination with pharmacotherapy was more effective than Brief Supported Psychotherapy (BSP) in combination with pharmacotherapy or pharmacotherapy alone after 12 weeks of treatment. In addition, the mean dose of 12.5 sessions of CBASP reported by Kocsis et al[11] may have been inadequate, as suggested by a recent meta-analysis of Cuijpers et al[6]. These authors reported that at least 18 treatment sessions are needed for patients with chronic depression to realize optimal effects of psychotherapy. In our study, 24 sessions of CBASP appeared to be an optimal number of sessions to test the effectiveness of CBASP during an extended follow-up period.

The fact that we found no overall effect for CBASP when compared to CAU could be due to the "high standard" of CAU provided in this study. CAU was offered according to the Dutch Depression Guidelines[25], in which combination treatment is recommended for chronic depression. Psychotherapy in the CAU cell consisted mostly of CBT, IPT, or SPSP applied by trained and certified professionals. Our finding that the effect of CAU only lasted until the end of the acute phase of treatment could be due to the fact that these approaches were not designed specifically for chronic depression; rather, they were originally designed to treat acute, episodic depression.

We must note that our response and remission rates in CBASP and especially in CAU are somewhat smaller than those reported in other studies.[6,8,11] One likely explanation for these differences is the fact that response and remission rates typically decrease as research moves from efficacy (clinical trials conducted in academic settings) to effectiveness, (clinical trials conducted in regular mental health care).[30] In future studies, these differences may be shown to be a reliable outcome phenomenon in pragmatic-applied clinical trials.

Our study had a number of strengths including the achievement of high external validity due to our pragmatic-applied design - a design that reflects the real-world complexity of chronically depressed patients who seek treatment for depression in the Netherlands; secondly, we obtained a rigorously diagnosed sample. The third strength was realized in that patients were randomly assigned to treatment conditions; fourthly, CBASP was compared to an active control group; finally, the employment of both interview and self-report measures of depression was administered.

However, the study also had several limitations. First, a significant proportion of participants did not complete treatment (30%) which, unfortunately, is a phenomenon prevalent among chronically depressed patients.[4] Although we used data analytic techniques that made use of all data up to the point of drop-out, we could not rule out the possibility that our findings were biased in unknown ways by early attrition; however, no differences on baseline demographic and clinical variables between the completers and noncompleters were obtained and the number of drop-out was the same in both groups. Secondly, a longer follow-up period would have been necessary to determine if the long-term effects of CBASP treatment will survive over an extended period.

In summary, these data suggest that CBASP is, in the long run, more effective than standard evidenced-based treatments for chronically depressed patients. The results are important as this is the first time CBASP has been tested rigorously with predominantly treatment-resistant patients who were referred to mental health care organizations and comparatively tested against a "high standard" active treatment control condition. Our data suggest that the added effectiveness of CBASP only becomes apparent after the acute treatment phase period ends. We opine that this finding is an important consideration for psychotherapy researchers in future clinical trials.

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