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Integrated cognitive behavioral therapy for ADHD in adult substance use disorder patients: Results of a randomized clinical trial

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ABSTRACT

Background: Attention Deficit Hyperactivity Disorder (ADHD) frequently co-occurs with Substance Use Disorders (SUDs). Standard ADHD pharmacotherapies are not effective in patients with this comorbidity and cognitive behavioral therapy (CBT) has not been tested in this population. This RCT aimed to compare the efficacy of Integrated CBT (CBT/Integrated) directed at adult ADHD and SUD with CBT directed at SUD only (CBT/SUD) in patients with SUD and ADHD (SUD + ADHD).

Methods: Randomized clinical trial among 119 SUD + ADHD patients in a SUD treatment center. CBT/Integrated consisted of 15 individual sessions of motivational therapy, coping skills training and relapse prevention for SUD, and training of planning skills, problem-solving skills and dealing with emotions for ADHD. CBT/SUD consisted of 10 individual SUD treatment sessions only. Primary outcome was ADHD symptom severity according to the ADHD rating scale (ARS) at post-treatment. Secondary outcomes included ADHD symptom severity after two-month follow-up, and treatment response (≥30% ADHD symptom reduction), substance use, depressive or anxiety symptoms, and quality of life at post-treatment and follow-up.

Results: CBT/Integrated was more effective than CBT/SUD in the reduction of ADHD symptoms post-treatment: ARS = 28.1 (SD 9.0) vs. 31.5 (SD 11.4) ($F = 4.739$, $df = 1, 282$, $p = .030$; $d = 0.34$). At follow-up, CBT/Integrated still resulted in lower ARS scores than CBT/SUD, but the difference was not significant at the 0.05 level. For other secondary outcomes, including substance use, no significant between-group differences were present.

Conclusions: Compared to regular SUD cognitive behavioral therapy, integrated cognitive behavioral therapy resulted in a significant extra improvement in ADHD symptoms in SUD + ADHD patients.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) affects around 4–5% of the adult population (Kessler et al., 2006). It is associated with a range of adverse outcomes, such as a negative influence on educational, occupational and social functioning, and higher risk of psychiatric hospitalization, incarceration, and premature death (Dalsgaard et al., 2015; Klein et al., 2012). The most widely investigated treatment modality for adult ADHD is (stimulant) medication, with a moderate to large effect size in different meta-analyses of 0.57–0.72 (Epstein et al., 2014; Meszaros et al., 2009; Castells et al., 2011). Cognitive Behavioral Therapy (CBT) is another important treatment modality for ADHD (National Institute for Health and Clinical Excellence, 2009). Several RCTs with CBT (mostly as an add-on to medication) have shown efficacy in patients with adult ADHD (Emilsson et al., 2011; Safren et al., 2010; Solanto et al., 2010; Weiss et al., 2012; Young et al., 2015, 2016), although one study failed to show benefit for group CBT over individual clinical management (Philipsen et al., 2015).

In patients with Substance Use Disorder (SUD), ADHD is a highly comorbid disorder, with reported prevalences of adult ADHD in treatment seeking SUD patients up to 31.3% (Van de Glind et al., 2014; Van Emmerik-van Oortmerssen et al., 2012). ADHD negatively affects SUD prognosis and treatment outcome: SUD + ADHD patients start abusing substances at a younger age, use more substances, are hospitalized

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more often (Arias et al., 2008) and have more relapses (Ercan et al., 2003) than SUD patients without ADHD. Vice versa, in patients with ADHD, SUD problems are common as well and range from 40 to 50%, with ADHD patients having a fourfold greater risk of SUD than people without ADHD (Fayyad et al., 2007). In contrast to the large effect sizes of pharmacotherapy in ADHD patients in general, the effects of pharmacotherapy in ADHD patients with comorbid SUD are inconclusive, with several studies reporting that stimulant medication has small or no effects on either ADHD symptoms or substance use (Castells et al., 2011; Wilens et al., 2012). A meta-analysis comparing ADHD medication with placebo reported an overall estimated effect size on ADHD symptoms in these patients of 0.30 (Cunill et al., 2015). Still, two recent studies reported positive effects with high dose stimulant treatment (Konstenius et al., 2014; Levin et al., 2015). Apart from efficacy, there are also concerns about using stimulant medication in SUD patients in terms of possible abuse, dependence and diversion (Bright, 2008).

Until now, it is unknown whether CBT for ADHD is effective in this comorbid patient group, because in all studies of CBT for adult ADHD, SUD patients were excluded (Emilsson et al., 2011; Safren et al., 2010; Solanto et al., 2010; Weiss et al., 2012; Young et al., 2015; Philipsen et al., 2015). This means that for a large number of patients, who may be treated in a broad range of healthcare settings, it is currently unclear if there is an effective treatment for their problems.

To investigate the possible benefit of a specific psychotherapeutic approach targeting ADHD symptoms in SUD patients, we developed an individually delivered integrated cognitive behavioral therapy as add-on to regular SUD treatment that mainly focuses on motivation, coping and SUD relapse prevention. For the integrated therapy, we used elements of an evidence-based ADHD psychotherapy developed by Safren et al. (2005a, 2005b). Here we report on the results of the first randomized controlled trial that assessed the efficacy of integrated CBT (CBT/Integrated) versus regular SUD treatment (CBT/SUD) in patients with both disorders. Our primary hypothesis is that CBT/Integrated directed at both ADHD and SUD outperforms CBT/SUD in these patients in its effect on the number of ADHD symptoms post-treatment. In addition, we hypothesize that CBT/Integrated outperforms CBT/SUD in its effects on the number of ADHD symptoms and in percentage of ADHD treatment responders at two-months-follow-up, and on the amount of substance use, depressive and anxiety symptoms, and quality of life at post-treatment and at two-months follow-up.

2. Methods

2.1. Design

This was a two-arm open-label parallel-group randomized controlled trial conducted in the Netherlands, registered in www.clinicaltrials.gov as NCT01431235. The study design including a detailed overview and discussion of interventions, assessment instruments and statistical analyses has already been published (Van Emmerik-van Oortmerssen et al., 2013)00

The study was approved by the ethics committee of the Academic Medical Centre in Amsterdam. All participants provided written informed consent. No reimbursements were provided for study participation.

2.2. Participants

Participants were enrolled between 2011 and 2016, with follow-up measurements between 2012 and 2016. All participants were referrals seeking treatment for their substance use problems at the Jellinek Addiction Treatment Center in Amsterdam, the Netherlands. Inclusion criteria were: after intake allocated to outpatient treatment, aged 18–65 years, Dutch speaking, current DSM-IV diagnosis of any substance use disorder other than nicotine dependence only, a comorbid DSM-IV diagnosis of adult ADHD, and written informed consent provided. Patients with (a history of) severe neurological (e.g., dementia, Parkinson's disease) or severe psychiatric disorders (e.g., psychosis, bipolar disorder) and patients with a borderline personality disorder were excluded from the study because other treatment programs were deemed more appropriate.

2.3. Procedures

Diagnostic assessment of SUD (CIDI) (World Health Organization, 1997) and screening for adult ADHD (Adult ADHD Self-Report Scale) (Daigre Blanco et al., 2009; Kessler et al., 2005) took place at treatment intake. Patients who screened positive for adult ADHD were invited for a diagnostic assessment of ADHD (CAADID) (Epstein et al., 2000). If a patient met criteria for adult ADHD and was willing to participate in the study, the baseline assessment took place.

All included patients started with Phase I of the treatment, i.e., four weekly SUD treatment sessions, designed to stop or at least reduce substance use. At the end of Phase 1, the diagnostic assessment of ADHD was repeated, to evaluate whether ADHD symptoms and the diagnosis adult ADHD were still present during abstinence, anticipating a potential change in symptoms after intoxication or withdrawal effects had disappeared.

Patients with a reconfirmed diagnosis of adult ADHD at the end of Phase I were randomized to either one of two CBT treatment arms in Phase II: integrated treatment (CBT/Integrated) aimed at treatment of both ADHD and SUD or Treatment as Usual (CBT/SUD) aimed at the treatment of SUD only.

After treatment, post-treatment assessments were performed, and follow-up assessments took place two months after. Assessments took place face-to-face, but since we foresaw a high proportion of drop-outs due to the pathology of these patients (with high levels of impulsivity and motivational difficulties), we offered the opportunity of post-treatment and follow-up assessments by telephone, in which only the main outcome data were collected (ADHD rating scale and Time Line Follow Back for substance use, see below).

We included both patients with and without ADHD medication. Patients who already used ADHD medication at the start of the trial were asked to keep their dose stable during the study, and patients without medication were informed that the study treatments did not provide medication, at least until post-treatment. If a patient without ADHD medication preferred pharmacotherapy, he or she was excluded from this study and received medication outside the study.

2.4. Measures

2.4.1. Primary outcome measure

ADHD symptom severity at post-treatment, measured with the ADHD rating scale (ARS) (Kooij et al., 2008; DuPaul et al., 1998), was the primary outcome measure. The ARS is a self-report 18-item questionnaire, consisting of two subscales with 9 items each: inattention and hyperactivity/ impulsivity. Each item is scored on a 4-point Likert scale ranging from 0 to 3 with higher scores indicating greater severity. The primary outcome was difference in mean ARS total score at the end of treatment between the two treatment groups (see separate methods paper) (Van Emmerik-van Oortmerssen et al., 2013).

2.4.2. Secondary outcomes measures

Secondary outcome measures included the following *ADHD* measures: ARS total score at follow-up (two months after end of treatment), and treatment response defined as ≥ 30% ARS symptom reduction from baseline to post-treatment and two-months follow-up (for justification of 30% cut-off, see: Wilens et al. (2005) and Levin et al. (2015).

Other secondary outcome measures included differences in substance use between the two treatment groups at post-treatment and two-months follow-up, anxiety and depression symptoms, and quality of life.

Substance use was assessed with the self-report Time Line Follow Back method (TLFB) (Agrawal et al., 2008). In the analyses, we used the number of days with excessive use of the primary substance of abuse in the week before assessment; excessive use was defined as at least six standard drinks for men per day, at least four standard drinks for women per day (in the case of alcohol as the primary drug of abuse), more than one joint per day (in the case of cannabis as the primary drug of abuse), or any use of other illicit drugs. Although we originally proposed to use number of days of excessive use in the past two months (Van Emmerik-van Oortmerssen et al, 2013), we later (but before closure of the dataset) decided that a shorter time interval of one week would better reflect substance use at end of treatment as substance use in the past two months reflects substance use during treatment rather than at the end of treatment.

Depressive symptoms were assessed with the Beck Depression Inventory (BDI) (Beck and Steer, 1987), *anxiety symptoms* were assessed with the Beck Anxiety Inventory (BAI) (Beck et al., 1988), and *quality of life* was assessed with the 3-level EQ-5D (Van der Zanden et al., 2006). These are all self-report instruments. The EQ-5D health states were valued using health utilities obtained from a British representative sample (Dolan, 1997).

2.5. Interventions / treatment programs

Integrated Treatment (*CBT/Integrated*) is an individually delivered CBT, designed to treat both ADHD and SUD. It consists of 15 weekly sessions. The first four sessions (phase I) dealt with SUD topics only, and the remaining 11 sessions (phase II) dealt with both SUD and ADHD topics. The SUD part consisted of motivational interviewing, coping skills training and relapse prevention, whereas the ADHD part mainly consisted of planning skills training (see also Table 1 for an overview of the treatment sessions). The SUD treatment elements are based on the Motivational Enhancement Therapy manual and Cognitive Behavioral Coping skills training manual used in project MATCH (Kadden et al., 1994; Miller et al., 1994) The ADHD treatment elements are a short version of the CBT program 'Mastering your adult ADHD' developed by Safren et al. (2005a, 2005b).

CBT/SUD is an individually delivered CBT designed to treat SUD. It consisted of 10 sessions that, in this study, were delivered fortnightly after the fourth session to keep total treatment time similar to CBT/Integrated. The same SUD treatment elements were applied in CBT/SUD and in CBT/Integrated.

To control for therapist effects (Anderson et al., 2009), the six participating therapists were involved in both treatments. All had extensive experience in CBT for SUD and had received additional training for the ADHD treatment part. They all participated in weekly supervision sessions provided by the same supervisor for both CBT/Integrated and CBT/SUD during the trial.

2.6. Randomization

Treatment allocation was performed by online application of a biased-coin randomization (minimization), ensuring that groups were balanced with respect to three baseline characteristics: gender, use of ADHD medication (yes/no) and type of SUD diagnosis (alcohol only/all other). Randomization was performed by study staff and the results were open to study staff, therapists and patients.

2.7. Data analysis

Data were analyzed according to the pre-defined analysis plan (Van Emmerik-van Oortmerssen et al., 2013). All analyses followed an intention-to-treat approach. Before conducting outcome analyses, we compared patients in the CBT/Integrated and CBT/SUD subgroups on baseline demographic variables, clinical characteristics, and medication utilization, using Chi-square analyses for categorical and *t*-tests for continuous variables.

Primary analyses then examined post-treatment outcomes by comparing CBT/Integrated and CBT/SUD using a Generalized Linear Mixed Model regression analysis (GLMM). To model baseline variance, we fitted a random intercept model in which the score on the outcome measures was used as the dependent variable and treatment condition, time, and treatment condition by time interaction were included as predictors (fixed effects). The three variables used in the minimization procedure (gender, use of ADHD medication at baseline, and type of SUD diagnosis) were also included as fixed effects. GLMM was also used for the analyses of the secondary outcome variables, except for the binary ADHD treatment response outcome, for which a Generalized

Table 1
CBT/Integrated and CBT/SUD treatment programs: an overview.

	CBT/SUD	CBT/Integrated
Session 1	Introduction, advantages and disadvantages of substance use, effect of substance use on mental problems, enhancing motivation to become abstinent	Introduction, advantages and disadvantages of substance use, effect of substance use on mental problems, enhancing motivation to become abstinent
Session 2	Treatment goals and treatment plan	Treatment goals and treatment plan
Session 3	Self-control measures	Self-control measures
Session 4	Risk situations	Risk situations
Session 5	Analysis of functional elements in substance use	*ADHD: introduction of a cognitive model of ADHD, introduction of calendar and task list in notebook*
Session 6	Dealing with craving	Analysis of functional elements in substance use (similar to session 5 in CBT/SUD)
Session 7	Relapse and relapse prevention	*ADHD: problem solving*
Session 8	Social pressure	Dealing with craving (similar to session 6 in CBT/SUD)
Session 9	Optional theme: one of earlier themes can be repeated, or one of the themes 'changing of thoughts' or 'dealing with emotions' can be explored.	*ADHD: reducing distractibility*
Session 10	Evaluation	Relapse and relapse prevention (Similar to session 7 in CBT/SUD)
Session 11		*ADHD: mood problems*
Session 12		Social pressure (similar to session 8 in CBT/SUD)
Session 13		*ADHD: organizing paperwork*
Session 14		Optional theme: one of earlier themes can be repeated, or one of the themes 'changing of thoughts' or 'dealing with emotions' can be explored. (similar to session 9 in CBT/SUD)
Session 15		Evaluation (Similar to session 10 in CBT/SUD)

Estimating Equation model (GEE) was fitted. Most continuous variables showed (near) normal distributions according to the Q-Q plot of the residuals around each mean, and thus a normal probability distribution was used in the analyses, except for substance use (number of days of excessive use), which was skewed to the right and for which a negative binomial model with log link was chosen. For treatment response, a GEE with binomial distribution, logit link function and exchangeable working correlation matrix was fitted. In this GEE Model, gender, use of ADHD medication at baseline, and type of SUD diagnosis were added as covariates.

Effect sizes of primary and secondary outcomes were calculated based on estimated means and associated standard deviations using Cohen's d; an effect size $d < 0.30$ is considered as not clinically relevant; $d = 0.30–0.50$ as a small effect; $d = 0.50–0.80$ as a moderate effect, and $d > 0.80$ as a large effect. All analyses were performed with SPSS, version 22 (SPSS Inc), with two-sided $\alpha = 0.05$.

Our a-priori power analysis was performed with G*power, using an expected effect size of $d = 0.5$ (moderate effect), two-sided $\alpha = 0.05$ and power = 0.80. Given these parameters, 65 patients were needed in each condition. We aimed for 150 patients, anticipating a 15% drop-out.

3. Results

3.1. Sample description and baseline comparisons

A total of 184 patients were enrolled into the study. Fifty-five of them (29.9%) stopped treatment and study participation during Phase I of the study, i.e., before randomization. Another 10 patients (5.4%) were not randomized due to other reasons (e.g., the ADHD diagnosis was not confirmed, patients withdrew consent, see Fig. 1), resulting in a total of 119 randomized patients (see Fig. 1 for information about patient flow). A total of 60 patients were randomized to CBT/Integrated of whom 48 (80%) participated in the post-treatment assessment and 39 (65%) participated in the follow-up assessment. A total of 59 patients were randomized to CBT/SUD of whom 46 (78%) participated in the post-treatment assessment and 39 (66%) participated in the follow-up assessment. For study drop-outs, post-treatment and/or follow-up assessments were missing in spite of repeated attempts of the investigators to contact these patients for further assessments.

Sociodemographic and clinical characteristics of the randomized and non-randomized samples are summarized in Table 2. There were no significant differences between the patients in CBT/Integrated and CBT/SUD at baseline, but patients who were randomized more often used alcohol as their only substance of abuse, had fewer days with excessive substance use, were better educated and had more inattention symptoms than non-randomized patients. Four patients (6.7%) in the CBT/Integrated group and one patient (1.7%) in the CBT/SUD group used ADHD stimulant medication at baseline; their prescription was unchanged during the study. Three patients started ADHD stimulant medication between post-treatment and follow-up (two patients (3.3%) in CBT/Integrated and one patient (1.7%) in CBT/SUD).

3.2. Treatment adherence and follow-up

Treatment adherence was good and not significantly different for both treatment groups with 41 patients (68.3%) attending at least 70% of the 15 treatment sessions (mean 12.1, SD 3.7 sessions) in the CBT/Integrated group and 47 patients (79.7%) attending at least 70% of the 10 treatment sessions (mean 8.5, SD 2.0 sessions) in the CBT/SUD group (Table 3).

Attendance rates for post-treatment and follow-up assessments were also similar for both treatment groups: 79.0% and 65.5% of all randomized patients, respectively. Although we planned to perform follow-up measures two months after post-treatment assessment, the mean time between post-treatment and follow-up was somewhat longer: 89.1 and 77.5 days in CBT/Integrated and CBT/SUD, respectively. This was a result of rescheduling appointments when patients did not show up.

3.3. Treatment outcomes

Table 4 presents the results of the generalized linear mixed models for the primary and secondary continuous outcomes.

3.3.1. Primary outcome

For the primary outcome, ARS total score, patients in both groups showed marked improvements reflected by a statistically significant effect of time in the analyses ($p < .001$). More importantly, there was a significant between group difference in the estimated mean of the ARS total score at post-treatment: 28.09 (SD 9.01) for CBT/Integrated vs. 31.54 (SD 11.39) for CBT/SUD ($F = 4.739$, $df = 1, 282$, $p = .030$; $d = 0.34$). At follow-up, the between group difference in ARS total score was very similar to the between group difference at post-treatment in absolute terms, but just not statistically significant: 28.47 (SD 8.37) in CBT/Integrated vs. 31.29 (SD 10.37) in CBT/SUD ($F = 3.165$, $df = 1, 282$, $p = .076$; $d = 0.30$).

3.3.2. Secondary outcomes

Both at post-treatment and at follow-up, the percentage of ARS treatment responders was higher in the CBT/Integrated compared with the CBT/SUD group, but these differences were not statistically significant: OR = 1.58 (95% C.I. 0.64–3.90) and OR = 2.05 (95% C.I. 0.77–5.50), respectively (see Table 5). For the other secondary outcomes, TLFB, BDI, BAI, and EQ-5D, patients in both groups showed improvements reflected by a statistically significant effect of time in all analyses ($p < .001$). Within-group treatment effect sizes ranged from 0.31 (Beck Anxiety Inventory in CBT/SUD at post-treatment) to 0.57 (Beck Depression Inventory in CBT/Integrated at post-treatment). However, no significant between-group differences were present at post-treatment or follow-up for these secondary outcomes (Table 4).

4. Discussion

This study was the first RCT investigating the efficacy of integrated CBT for ADHD in adult patients who also had SUD. The results demonstrated that an extension of five extra CBT sessions specifically aimed at ADHD to a regular SUD therapy resulted in a significant extra reduction in ADHD symptoms at post-treatment in patients with both disorders. This finding is particularly notable, given that the control condition is already an effective treatment for SUD that also has CBT elements. A similar trend towards benefit for CBT/Integrated was present at the two-months follow-up, but the difference in ADHD symptom scores between the treatment conditions was just not statistically significant. We think that this was probably due to reduced power since the number of patients at follow-up was smaller. The standardized effect sizes at post-treatment and follow up were .34 and .30, representing small but clinically relevant effects. These effect sizes are smaller than in studies investigating the effect of CBT in ADHD patients without SUD (.60 in the study by Safren et al. (2010) and .65 in the study by Young et al. (2015)), but one should take into account that in these studies, ADHD interventions were tested against placebo-psychotherapy (relaxation and educational support) or medical management. The control condition in our trial consisted of active psychotherapy also based on CBT, and although SUD was the focus of treatment, several skills of planning and problem solving that are highly relevant for ADHD treatment were addressed in our CBT/SUD as well (Young and Sedgwick, 2015). In line with this, the within treatment effect size for ADHD symptoms in the CBT/SUD condition was .47 and in the CBT/Integrated condition even .83. Another important design feature is the fact that the ADHD treatment programs by Safren et al. (2010) and Young et al. (2015) consisted of 12 individual/15 group CBT sessions directed at ADHD, whereas our CBT/Integrated

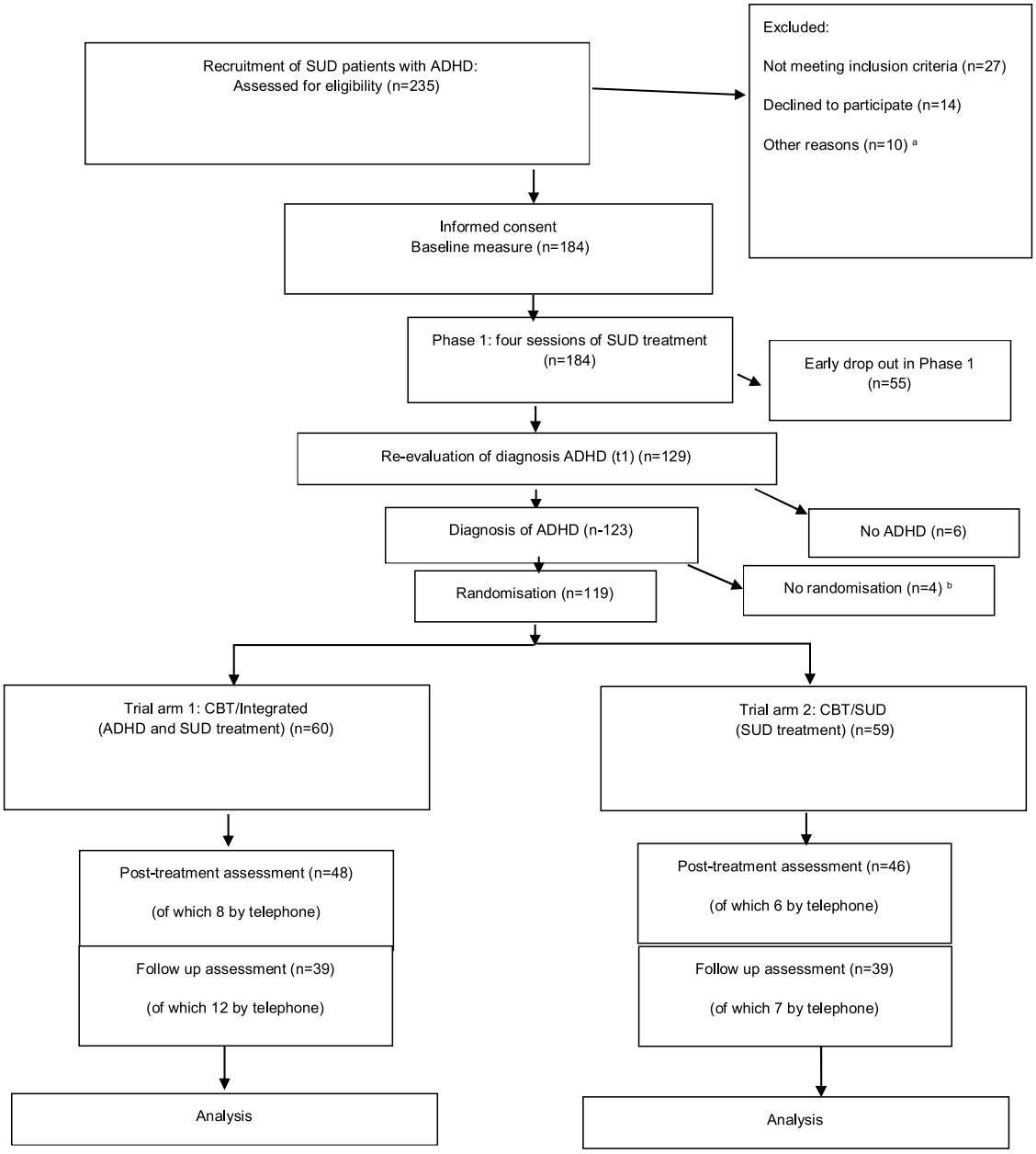

Fig. 1. Trial flowchart.
Note:
a) 10 patients who were assessed for eligibility were excluded for 'other reasons', most frequently 'not showing up anymore for baseline measure or therapy'.
b) 4 patients with a confirmed diagnosis of ADHD were not randomized due to the following reasons:
- one patient did not want to continue research activities.
- one patient did not want to continue treatment of SUD.
two patients were excluded because of a change of dose of ADHD medication after baseline.

intervention contained only five extra sessions for the treatment of ADHD. This condensed version already resulted in a significant effect on ADHD symptoms, over and above the already considerable effect of CBT/SUD. When comparing our study with the two earlier studies on CBT in ADHD patients without SUD, it should also be noted that patients in the former two studies had ADHD symptoms despite using ADHD medication. This is different from our study in which the vast majority of patients did not use any specific ADHD medication during the study or in the past; a situation that is consistent with the fact that for most of our SUD patients, active screening for ADHD for this trial was the first time their ADHD was actually recognized as such.

The effect sizes for ADHD symptoms that we found are very much in line with most pharmacological and psychological treatments for mental and substance use disorders (e.g., ES = .42 for psychotherapy in MDD and .26 for pharmacotherapy in alcohol use disorder (Huhn et al., 2014; Jonas et al., 2014; Cuijpers et al., 2010).

Contrary to our hypotheses, the results of all other secondary outcomes (substance use, depressive and anxiety symptoms, quality of life) did not differ significantly between treatment groups; patients in both treatment conditions improved significantly on all these measures, but there were no significant group differences. These results indicate the presence of a specific effect of CBT/Integrated on ADHD symptoms. Although the self-medication hypothesis (Mariani et al., 2014) poses that psychiatric symptoms such as ADHD symptoms maintain substance use, we found no effect of reduced ADHD symptoms on substance use at post-treatment and follow-up, but our follow-up time interval was

Table 2
Baseline sociodemographic and clinical characteristics: number, percentage or mean and standard deviation (SD).

	All randomized patients (n = 119)	Drop outs before randomization (n = 55)	P-value[a]	CBT/Inte-grated (n = 60)	CBT/SUD (n = 59)	P-value[b]
Age in years (SD)	35.1 (8.9)	33.3 (8.5)	.218	35.4 (8.8)	34.7 (9.1)	.675
Gender, No. male (%)	99 (83.2)	49 (89.1)	.310	50 (83.3)	49 (83.1)	.967
Married/ cohabitant (%)	46 (38.7)	18 (32.7)	.582	27 (45.0)	19 (32.2)	.154
Job status, No. employed (%)	95 (79.8)	37 (67.2)	.072	47 (78.3)	48 (81.3)	.820
Education[c]: highest completed education level, No. (%)	N = 118	N = 53		N = 59	N = 59	
Low	14 (11.9)	13 (24.5)	.008	9 (15.3)	5 (8.5)	.348
Average	39 (33.1)	24 (45.3)		17 (28.8)	22 (37.3)	
Higher	49 (41.5)	15 (28.3)		27 (45.8)	22 (37.3)	
Highest	16 (13.6)	1 (1.9)		6 (10.2)	10 (16.9)	
Primary substance of abuse, No. (%)						
Alcohol	57 (47.9)	16 (29.1)	.099	31 (51.7)	26(44.1)	.801
Cannabis	30 (25.2)	16 (29.1)		15 (25.0)	15 (25.4)	
Stimulants	28 (23.5)	20 (36.4)		12 (20.0)	16 (27.1)	
Opiates	0 (0.0)	1 (1.8)		0 (0.0)	0 (0.0)	
Other	4 (3.4)	2 (3.6)		2 (3.3)	2 (3.4)	
Substance status, No. (%) Alcohol only	31 (26.1)	2 (3.6)	.000	16 (26.7)	15 (25.4)	.877
Number of days of excessive[d] use of primary substance in past 60 days (SD)	31.1 (21.4)	38.8 (21.3)	.028	29.5 (19.9)	32.7 (23.0)	.419
Number of days of excessive[d] use in past week (SD)	2.88 (2.7)	3.8 (2.9)	.037	2.6 (2.6)	3.2 (2.8)	.179
ADHD diagnosis[e], No. (%)						
Inattentive subtype	63 (52.9)	N.A.	N.A.	33 (55.0)	30 (50.8)	.895
Hyperactive/ impulsive subtype	10 (8.4)			5 (8.3)	5 (8.5)	
Combined subtype	46 (38.7)			22 (36.7)	24 (40.7)	
ADHD rating scale[f] (SD)	31.8 (6.8)	30.3 (7.5)	.176	31.5 (6.3)	32.2 (7.3)	.574
Beck Depression Inventory[f] (SD)	16.4 (8.4)	16.3 (8.6)	.929	16.1 (8.8)	16.8 (8.1)	.647
Beck Anxiety Inventory[f] (SD)	13.9 (8.8)	14.9 (8.5)	.475	14.4 (9.0)	13.4 (8.5)	.547
EQ5D[g] (SD)	0.70 (.26)	0.74 (.23)	.340	0.69 (.27)	0.71 (.24)	.554
Use of ADHD medication at baseline[h], No. (%)	5 (4.2)	3 (5.5)	.714	4 (6.7)	1 (1.7)	.177

Note:
- Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; CBT/Integrated, Integrated Cognitive Behavioral Therapy; CBT/SUD, Cognitive Behavioral Therapy for Substance Use Disorders.
- [a]P value indicates comparison of randomized patients and patients who dropped out before randomization (*t*-test or Chi-square tests).
- [b]P value indicates comparison of patients in CBT/Integrated and CBT/SUD (*t*-test or Chi-square tests).
- [c]Highest completed educational level: low (primary school); average (lower general secondary education); higher (vocational education / higher general secondary education or pre- university education); highest (higher vocation education / academic education).
- [d]Excessive use is defined as ≥ 6 standard units a day in the case of alcohol for men, and ≥ 4 for women; > 1 joint a day in the case of cannabis, and any use on a day in the case of another drug.
- [e]At randomization.
- [f]Higher scores indicate more severe symptoms.
- [g]Higher scores indicate better health-related quality of life.
- [h]3 patients started medication after post-treatment measurements (2 patients in CBT/Integrated and 1 patient in CBT/SUD), apart from the patients that are reported in this table.

Table 3
Treatment attendance, assessment attendance and length of study period.

	CBT/Integrated (n = 60)	CBT/SUD (n = 59)	p-value
Treatment attendance			
Sessions (SD)	12.1 out of 15 (3.7)	8.5 out of 10 (2.0)	N.A.
≥70% treatment attendance[a], No. (%)	41 (68.3%)	47 (79.7)	.159
Assessment attendance, No. (%)			
Post-treatment	48 (80.0)	46 (78.0)	.785
Follow-up	39 (65.0)	39 (66.1)	.899
Length of study period in days (SD)			
Baseline until post-treatment	238.4 (92.6)	190.8 (64.8)	.005
Post-treatment until follow-up	89.1 (32.4)	77.5 (22.3)	.074

Note: a) i.e. 7 (CBT/Integrated) or 11 (CBT/SUD) sessions.

relatively short and the SUD component in both the CBT/Integrated and CBT/SUD already succeeded in reducing substance use. The fact that we did not find an effect of CBT/Integrated over CBT/SUD on quality of life might be related to the fact the EQ-5D was not able to catch the more subtle differences in functioning, as it comprised only one question on daily functioning at home, work and other activities, with 3 possible answers (normal functioning, some problems, or not able to function at all).

The current study has both strengths and limitations. The main strength of the study is its clinical relevance. Given the high prevalence of SUD in adult ADHD patients (and vice versa) and the lack of studies investigating the possible benefits of CBT programs in the treatment of comorbid disorders such as ADHD in SUD patients, this study makes an important contribution to the field. Furthermore, the scale of pharmacotherapy prescriptions for ADHD is the subject of a fierce societal debate, and it is important that also other treatment options are investigated and implemented if proven effective. In line with this, many ADHD patients with SUD prefer not to receive pharmacotherapy and CBT is often perceived as an appealing treatment option (McHugh et al., 2013). The repeated diagnostic assessment for ADHD is another strength of this study. Patients in the current trial had a stable diagnosis of adult ADHD that was not influenced by intoxication or withdrawal. The study also has some limitations. First, CBT/SUD consisted of 33% less treatment time than CBT/Integrated (10 vs. 15 sessions planned),

Table 4
Estimated means, within-treatment and between-treatment groups effect sizes of primary and secondary outcomes by treatment group at post-treatment and follow-up.

	CBT/Integrated				CBT/SUD				P values		Cohen's d	
Measure	Baseline mean (SD)	Post-treatment mean (SD)	Follow-up mean (SD)	Cohen's d (baseline to post-treatment) within treatment group)	Baseline mean (SD)	Post-treatment mean (SD)	Follow-up mean (SD)	Cohen's d (baseline to post-treatment) within treatment group	Post treatment (between treatment groups)	Follow up (between treatment groups)	Post-treatment (between treatment groups)	Follow-up (between treatment groups)
Primary outcome	N = 60	N = 48	N = 39		N = 59	N = 46	N = 39					
ARS total score	35.65 (9.30)	28.09 (9.01)	28.47 (8.37)	.83	36.78 (10.98)	31.54 (11.39)	31.29 (10.37)	.47	.030	.076	.34	.30
Secondary outcomes	N = 60	N = 48	N = 39		N = 59	N = 46	N = 39					
TLFB (days of excessive use in prior week)	1.47 (3.64)	0.28 (0.70)	0.51 (1.04)	.45	2.06 (5.30)	0.40 (0.95)	0.60 (1.24)	.44	.453	.690		
	N = 60	N = 40	N = 27		N = 59	N = 40	N = 32					
BDI	15.05 (12.55)	8.39 (10.56)	9.02 (9.51)	.57	15.66 (13.06)	9.87 (10.25)	10.00 (10.24)	.49	.366	.612		
BAI	15.83 (14.79)	10.07 (12.02)	10.28 (11.17)	.43	14.99 (16.05)	10.51 (13.09)	10.06 (12.73)	.31	.782	.906		
EQ-5D	0.75 (0.31)	0.88 (0.19)	0.88 (0.16)	.51	0.79 (0.38)	0.90 (0.25)	0.91 (0.23)	.34	.564	.536		

Note:
Reported in this table are the estimated means from the GLMM; these may differ from the observed means in Table 1. As a consequence, means of subscales of the ARS do not add up to the means of the total ARS scale.
Effect sizes are calculated based on estimated means and standard deviations.
Between treatment effect sizes are reported for variables with $p \leq .10$ only.
ARS = ADHD Rating Scale; TLFB = Time Line Follow Back; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory.

Table 5
Treatment response as a function of group status: results of GEE model comparing CBT/Integrated and CBT/SUD at post-treatment and follow-up.

	Treatment response[a,b]				
	CBT/ Integrated	CBT/SUD	Between group OR (95% C.I.)	P-value	NNT
Post-treatment	33%	24%	1.58 (0.64–3.90)	.318	11.1
Follow-up	34%	20%	2.05 (0.77–5.50)	.145	7.1

Note:
Estimated proportions based on the GEE model are reported.
Treatment response indicates at least 30% reduction in ADHD symptoms.
Abbreviations: GEE = Generalized Estimating Equation; NNT = number needed to treat.

and there is a possibility that the effect of CBT/Integrated on ADHD symptoms is a non-specific result due to more treatment time and attention in general. However, the results showed specific effects only on ADHD symptoms and not on other aspects of the co-existing psychopathology (e.g., depression, anxiety). Therefore, this explanation seems less likely. Another limitation is the fact that outcomes in this non-blinded trial were measured with self-report instruments. Again, the fact that significant positive results in favor of the experimental treatment were only observed in (specific) self-reported ADHD symptom scales and not in other self-reported psychopathological domains would argue against information bias as a likely explanation of the current findings. Moreover, in the RCT of Young et al. who studied CBT for adults with ADHD, the self-report outcomes were consistent with blinded-observer rated scales, which suggests that self-report of ADHD symptoms is a reliable measure (Young et al., 2015). Another limitation of the current study is the fact that we did not provide data on treatment fidelity/integrity. However, if contamination between treatments would have taken place, it would mean that elements of the ADHD intervention were also used in the control condition and that our findings would be an underestimation of the real effect. Furthermore, although treatments were planned to take approximately three months, in practice they often took much more time (238.4 days in CBT/Integrated and 190.8 days in CBT/SUD). This probably reflects the challenges of therapy with this population, with many patients missing and rescheduling appointments. Also, with 119 instead of the planned 130 randomized patients, this study was slightly underpowered which may have influenced the results and could, in particular, have resulted in type II error with regard to the effect on ADHD symptoms at follow-up. It is also important to keep in mind that in the current study, SUD patients with comorbid ADHD were recruited. These patients could be different from patients with a primary diagnosis of ADHD and comorbid SUD problems, both in terms of symptom severity and response to the current intervention. With respect to this limitation, it is important to keep in mind that the majority of the participants neither had a diagnosis of ADHD before engaging in this study, nor did they seek treatment for ADHD. This may have affected the results, as these patients might have been less motivated for ADHD treatment. Our clinical impression, however, was that many patients appreciated the offer of ADHD treatment. Finally, it should be noted that many SUD patients with ADHD left the study before randomization and that these patients had more severe SUD, were less educated and had less ADHD-related attention problems than the patients that were retained in the study. It is, therefore, possible that CBT/Integrated is less appealing for the most severe SUD patients with less education and especially attractive to SUD patients with an ADHD subtype with more attentional problems. Future research should focus on identifying means to reduce drop-out rates from this treatment and from addiction treatment in general. Other interesting topics for future research on the integrated treatment include the comparison between CBT/Integrated and pharmacological treatment of ADHD with (high dose) stimulants, or the effect of a combination of these two, the cost-effectiveness of CBT/Integrated, and the effect of extending the ADHD intervention by augmenting the number of sessions on ADHD treatment.

5. Conclusions

This is the first study demonstrating that integrating a shortened cognitive behavioral therapy for ADHD to regular SUD therapy in adults with both conditions is effective in reducing ADHD symptoms. With a modest investment in training and treatment time, CBT/Integrated is easy to implement and thus suitable for widespread implementation. The study also adds to the growing body of literature supporting non-pharmacological approaches to ADHD.

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Contributors

KvE, RS, WvdB and EV designed the study. KvE and FK managed data collection. Analyses were performed by KvE and MB. KvE, RS, and WvdB led the drafting of the manuscript. EV, FK and JD revised the manuscript. All authors contributed to and approved of the final version of this manuscript.

Conflict of interest

No conflict to declare.

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