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Prediction of drop-out and outcome in integrated cognitive behavioral therapy for ADHD and SUD: Results from a randomized clinical trial

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HIGHLIGHTS

- Drop-out from treatment is a major challenge in addiction treatment.
- Here, treatment drop-out was investigated in substance use disorder patients with ADHD.
- Patients with drug use disorder (instead of alcohol use disorder) have a higher drop-out risk.
- Lower functioning on a planning task is associated with a higher risk of drop-out.

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ABSTRACT

Background: Patients with substance use disorder (SUD) or Attention Deficit Hyperactivity Disorder (ADHD) have a high risk of drop out from treatment. Few studies have investigated predictors of therapy drop out and outcome in SUD patients with comorbid ADHD. Recently, integrated cognitive behavioral therapy (CBT/Integrated) was shown to be more effective than standard CBT (CBT/SUD) in the treatment of SUD + ADHD.
Objective: To investigate the association of demographic, clinical and neurocognitive variables with drop-out and treatment outcome, and to examine which of these variables are suitable for patient-treatment matching.
Methods: We performed an RCT in which 119 patients were allocated to CBT/Integrated (n = 60) or CBT/SUD (n = 59). In addition, 55 patients had dropped out before randomization. Demographic variables, clinical characteristics and measures of cognitive functioning (Stroop, Tower of London (ToL) and Balloon Analogue Risk Task (BART)) were included as predictors. Outcome measures were: early treatment drop-out, ADHD symptom severity, and substance use severity at end of treatment and follow up.
Results: Primary substance of abuse (drugs as opposed to alcohol only) and lower accuracy scores on the ToL were significant predictors of early treatment drop-out. Having more depression and anxiety symptoms and using ADHD medication at baseline significantly predicted more ADHD symptoms at end of treatment, and higher accuracy scores on the ToL significantly predicted higher substance use at end of treatment. No significant predictor-by-treatment interactions were found.
Conclusion: The results add to the existing realization that also relatively mild cognitive deficits are a risk factor for treatment drop-out in these patients.

1. Introduction

Substance use disorders (SUDs) are among the leading causes of morbidity and mortality worldwide (Degenhardt et al., 2013; Whiteford et al., 2013). They cause a great deal of personal suffering for patients and their loved ones and have devastating medical, social and economic effects (Degenhardt & Hall, 2012). Patients with SUD often have psychiatric comorbidities with adult Attention Deficit Hyperactivity Disorder (ADHD) being one of the most frequently encountered comorbid disorders (van de Glind et al., 2014; van Emmerik-van Oortmerssen

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et al., 2012). Although evidence-based pharmacological and psychotherapeutic interventions for both SUD and ADHD are available, very little is known about the efficacy of treatment for patients with both conditions. Standard pharmacological treatment has shown mainly negative outcomes (Carpentier et al., 2005; Konstenius et al., 2010; Levin et al., 2007, 2006; Riggs et al., 2011), but with two studies suggesting positive effects of high doses of stimulants (Konstenius et al., 2014; Levin et al., 2015). Recently, we have shown that integrated cognitive behavior therapy (CBT/Integrated) directed at both SUD and ADHD is more effective in these patients than standard CBT directed at SUD only (CBT/SUD) (van Emmerik-van Oortmerssen, Vedel, & Kramer, 2019). However, many patients dropped out from treatment and there was no difference between treatments in substance use outcome. An important question is whether it can be predicted which patients with SUD and ADHD are more likely to drop out of treatment, and also whether it can be predicted which patients have a higher probability of negative outcomes.

1.1. Predictors of treatment drop-out and treatment outcome in SUD treatment

1.1.1. Predictors of treatment drop-out in SUD treatment

Treatment completion has been proposed as an important factor related to favorable outcomes of addiction treatment. Treatment drop-out is common with reported drop-out rates ranging from about 20% to 60% (Brorson, Ajo Arnevik, Rand-Hendriksen, & Duckert, 2013). In a systematic review, Brorson et al. (2013) found conflicting results for a range of patient, treatment and process characteristics, but consistent findings for cognitive deficits, low treatment alliance, comorbid personality disorder (antisocial/histrionic) and younger age. The link between treatment adherence and general cognition has been confirmed in many studies (Dominguez-Salas, Diaz-Batanero, Lozano-Rojas, & Verdejo-Garcia, 2016). This is important because many SUD patients may suffer from (mild) neurocognitive impairments (Aharonovich, Brooks, Nunes, & Hasin, 2008) either as a pre-existing risk factor or as a result of chronic alcohol and/or drug use. In alcohol dependent patients for instance, deficits on neuropsychological tests are present in 50–80% (Bates et al., 2004). These impairments interfere with retention in and outcome of SUD treatment as they affect the ability to learn new information, integrate new skills and plan and implement behavioral strategies as alternatives to substance use (Bates, Pawlak, Tonigan, & Buckman, 2006). Only very few studies have examined treatment-related factors such as treatment method (Marissen, Franken, Blanken, van den Brink, & Hendriks, 2007) or treatment intensity (Curran, Stecker, Han, & Booth, 2009) as predictors of drop-out and therefore no firm conclusion can be drawn on this subject. In addition, several studies have found that drop-out in different treatment modalities was moderated by certain demographic risk factors such as age (Brorson et al., 2013).

1.1.2. Predictors of treatment outcome in SUD treatment

Treatment outcome (including abstinence and reduced substance use) is – amongst others – predicted by impairments in decision-making (Iowa Gambling Task), attentional bias and baseline impulsivity (Dominguez-Salas et al., 2016; Nuijten et al., 2016; Stevens et al., 2014). Interestingly, Passetti et al. found that deficits in decision making only influenced outcome in an outpatient setting, but not in inpatients (Passetti, Clark, & Davis, 2011).

1.2. Predictors of treatment drop-out and outcome in ADHD treatment

1.2.1. Predictors of treatment drop-out in ADHD treatment

In contrast to the many studies on drop-out from addiction treatment, relatively little is known about factors involved in treatment drop-out in patients with adult ADHD. Studies have mainly focused on medication non-adherence, which is reported to be around 50% (Caisley & Muller, 2012). Factors associated with medication non-adherence include age (Ahmed and Aslani, 2013; Frank et al., 2015; Treuer et al., 2016), gender (Treuer, Mendez, Montgomery, & Wu, 2016), comorbid psychiatric disorders (Ahmed and Aslani, 2013; Treuer et al., 2016; Gift et al., 2016; Torgersen et al., 2012; Victor et al., 2009), and medication related factors such as type of medication (Caisley & Muller, 2012), adverse effects (Castells et al., 2013; Ahmed and Aslani, 2013; Frank et al., 2015), and lack of efficacy (Ahmed and Aslani, 2013; Gajria et al., 2014). In several trials of CBT for ADHD patients drop-out rates were low: 8% treatment drop-out in the study by Safren, Sprich, and Mimiaga (2010) and 20% in the study by Solanto, Marks, and Wasserstein (2010) but no information was reported on factors associated with drop-out.

1.2.2. Predictors of treatment outcome in ADHD treatment

Although several authors argue that in the future, genetic information (Stein & McGough, 2008) and neurocognitive measures (Hermens, Rowe, Gordon, & Williams, 2006) may be used in the prediction of pharmacological treatment response and in personalizing treatment for ADHD, this is not yet the case. To date, the literature on predictors of treatment outcome and patient-treatment matching in ADHD is very limited. Comorbidity of ADHD with SUD and with personality disorders was associated with lower treatment response in methylphenidate treatment in a study by Retz and Retz-Junginger (2014). With regard to predictors of psychological treatment for (adult) ADHD there are even fewer studies. We found only one study that explored treatment matching of CBT programs for adolescents with ADHD, where a planning intervention outperformed solution focused therapy in a subgroup of patients with comorbid anxiety symptoms but low depression levels (Boyer et al., 2016).

1.3. Predictors of drop-out and outcome in the treatment of SUD + ADHD patients

Several studies report that comorbid ADHD is associated with less optimal outcomes in SUD treatment (Levin et al., 2004). However, very little is known about risk factors related to drop-out or treatment outcome in SUD + ADHD patients. We found one study among adolescents with SUD and ADHD that showed substance use, ADHD symptom severity at baseline, conduct disorder, and court-mandated status to be related to outcome (Tamm, Trello-Rishel, & Riggs, 2013), but no such data on adults were found.

When summarizing the existing literature, we conclude that although many studies have looked at predictors for drop-out and outcome in SUD patients, there is only minimal information on predictors of drop-out and outcome in SUD + ADHD patients. In a recent RCT we showed that CBT/Integrated is effective in reducing ADHD symptoms (van Emmerik-van Oortmerssen et al., 2019). Still, we do not know whether this treatment is equally effective for all patients, or whether certain patient characteristics differentially affect treatment outcome. Finally, we found no overall difference on SUD outcome between the treatments, but differential benefits may exist for certain patient groups and the lack of an overall effect may be the result of opposing outcomes in different subgroups, i.e. some of the patients getting better and others getting worse with the new treatment. Therefore, the current study first examined the predictive value of demographic variables, clinical characteristics and aspects of cognitive functioning on overall treatment drop-out of patients with SUD and ADHD. Because we were struck by the fact that the vast majority of drop-out occurred in the first phase of treatment, often after one or two treatment appointments, we focused on this early treatment drop-out, although in the literature we did not find a particular distinction between different forms of drop-out. Second, we examined which patient characteristics were associated with a positive treatment outcome in CBT/Integrated. Additionally, we examined whether certain variables differentially predicted outcomes of CBT/Integrated compared with CBT/SUD (patient-treatment

matching).

2. Material and Methods

2.1. Design

This study was designed as an open-label, parallel-group, randomized controlled trial. After screening and baseline assessment, participants were randomly assigned to the experimental group (CBT/Integrated, consisting of 15 CBT sessions to treat SUD and ADHD) or the control group (CBT/SUD, consisting of 10 CBT sessions to treat SUD). Randomization was performed by online application of a biased-coin randomization, aiming to balance trial arms with respect to gender, SUD diagnosis (alcohol only versus other substances), and the use of ADHD medication (yes/no). For detailed information about the procedure, see van Emmerik-van Oortmerssen, Vedel, and Koeter (2013).

The study was approved by the medical ethics committee of the Academic Medical Centre in Amsterdam and all participants provided written informed consent. The study is registered in the Clinical Trial Register (www.clinicaltrials.gov NCT01431235).

2.2. Participants

Eligible patients were referrals seeking treatment for substance use problems at the Jellinek, a large addiction treatment center in Amsterdam, The Netherlands. Inclusion criteria were: age 18–65 years, full command of the Dutch language, current DSM-IV diagnosis of any substance use disorder other than only nicotine dependence, a comorbid DSM-IV diagnosis of adult ADHD, and after intake allocated to outpatient treatment. Patients were excluded if they suffered from a severe neurological or psychiatric disorder (e.g. psychosis), or if they had a comorbid diagnosis of borderline personality disorder.

2.3. Procedure

New patients were assessed for eligibility in the intake procedure. Then, at inclusion, baseline data were collected. Subsequently, participants started with Phase I of treatment, which consisted of the first four CBT treatment sessions, all of which were aimed at the treatment of SUD. Then, randomization took place for Phase II of the treatment, including either 11 sessions CBT/Integrated or 6 sessions CBT/SUD). At the end of treatment, post-treatment measures were administered in a separate appointment usually one week after the last therapy session, and follow-up measures were performed two months later.

The order of the test administration was the same for all participants. Abstinence from alcohol or drugs was no prerequisite to participate. Sobriety was not measured prior to therapy appointments.

A total of 174 patients were included in this study; their data were used in the analyses of early Phase I drop-out (which comprises the first four treatment sessions, i.e. before randomization took place). A total of 119 patients were randomized and included in the treatment outcome analyses. In the original RCT, 184 patients were included, 10 of whom were neither early drop-outs nor randomized for different reasons; their data were not used in this study.

2.4. Treatments

CBT/Integrated consisted of 15 individually-delivered weekly CBT sessions. The outline of the treatment protocol is published elsewhere (van Emmerik-van Oortmerssen et al., 2013). Every session dealt with a predefined topic, with 5 sessions on ADHD-related topics, and 10 sessions for the treatment of SUD. CBT/SUD consisted of these 10 sessions for the treatment of SUD only. In both treatments, the first 4 sessions (Phase 1 of treatment) were the same and dealt with SUD treatment only. Both treatments were provided by trained, experienced therapists.

2.5. Assessments/measures

2.5.1. Eligibility

The Composite International Diagnostic Interview (CIDI) (Organization, 1997) was used for diagnostic assessment of SUD, the first six items of the Adult ADHD Self-Report Scale (ASRS-v1.1) (Kessler, Adler, & Ames, 2005) were used to screen patients for ADHD, and Conners' Adults ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein, Johnson, & Conners, 2000) was used to diagnose ADHD.

2.5.2. Predictors

- Sociodemographic data on age, gender, job status, highest educational level and relationship status were retrieved at baseline.
- Type of SUD (alcohol only, or other) was determined according to the CIDI.
- Subtype of ADHD was determined according to the CAADID.
- Information on the use of ADHD medication (yes/no) at baseline was obtained.
- Baseline severity of ADHD symptoms were assessed with the ADHD rating scale (Kooij et al., 2008).
- Severity of alcohol and drug use in the two months before referral to treatment was measured using the Time Line Follow Back (TLFB) procedure (Agrawal, Sobell, & Sobell, 2008). From this measure, only the number of days with heavy use in the past week was used. Heavy use was defined as at least six standard units of alcoholic beverages for men per day, at least four for women (in the case of alcohol as the primary drug of abuse), more than one joint per day (in the case of cannabis being the primary drug of abuse), or any use of other illicit drugs.
- Depressive and anxiety symptoms at baseline were assessed with the Beck Depression Inventory (BDI) (Beck & Steer, 1987) and the Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988).
- Spatial planning abilities were measured with a computerized *Tower of London (ToL)* task (van den Heuvel et al., 2003). In this task, the participant had to sort balls of three different colors on sticks of different lengths into a specified pattern. In the computerized version, the balls cannot actually be moved, but for each trial the participant had to plan and count how many steps are necessary to place the balls in a correct way. The complexity of the task differed from one to six steps. Patients had a limited time of 60 s to answer each trial. The main outcome variable of this task was the accuracy or the number of correct responses, calculated as a weighted sum that takes into account the difficulty of each trial. In addition, latency or average time needed per trial to give a response was used (reaction time).
- Cognitive interference and selective attention was measured with a computerized version of the classic *Color-Word Stroop task* (Cox et al., 2006; Schmaal et al., 2013). In this task, congruent color words and incongruent color words (e.g. the word 'red' written in green ink) were presented; participants were instructed to respond via the keyboard, as quickly and accurately as possible, to the color in which each word was printed, while attempting to ignore reading the word. The interference score was calculated by subtracting the mean reaction time on the congruent stimuli from the mean reaction time on the incongruent stimuli for all correct trials. In addition, accuracy (i.e. the percentage of correct responses) on the congruent trials and accuracy on the incongruent trials were used.
- Risk taking propensity, conceptualized as the interaction between poor impulse control and heightened reward seeking (Ryan, Mackillop, & Carpenter, 2013), was assessed with the *Balloon Analogue Risk Task (BART)* (Lejuez, Read, & Kahler, 2002). In this computerized task, risky choices lead to positive consequences to a certain point, with further excessive risk taking leading to greater negative consequences. In this task, a small balloon was presented, which could be inflated by pressing on the balloon pump. With each

Table 1
Baseline sociodemographic, clinical and neurocognitive characteristics: number, percentage or mean and standard deviation (SD).

	All randomized patients (n = 119)	Drop outs before randomization (n = 55)	CBT/Integrated (n = 60)	CBT/SUD (n = 59)	P-value[a]
Age in years (SD)	35.1 (8.9)	33.3 (8.5)	35.4 (8.8)	34.7 (9.1)	0.675
Gender, No. male (%)	99 (83.2)	49 (89.1)	50 (83.3)	49 (83.1)	0.967
Married/ cohabitant (%)	46 (38.7)	18 (32.7)	27 (45.0)	19 (32.2)	0.154
Job status, No. employed (%)	95 (79.8)	37 (67.2)	47 (78.3)	48 (81.3)	0.820
Education: highest completed education level[b], No. (%)	N = 118	N = 53	N = 59		
Low	14 (11.9)	13 (24.5)	9 (15.3)	5 (8.5)	0.348
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)	31 (51.7)	26 (44.1)	0.801
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)	
Primary substance of abuse, No. (%)					
Alcohol only	31 (26.1)	2 (3.6)	16 (26.7)	15 (25.4)	0.877
Substance use severity: number of days of excessive[c] use in past week (SD)	2.88 (2.7)	3.8 (2.9)	2.6 (2.6)	3.2 (2.8)	0.179
ADHD diagnosis[d], No. (%)					
Inattentive subtype	63 (52.9)	N.A.	33 (55.0)	30 (50.8)	0.895
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[e] (SD)	31.8 (6.8)	30.3 (7.5)	31.5 (6.3)	32.2 (7.3)	0.574
Beck Depression Inventory[f] (SD)	16.4 (8.4)	16.3 (8.6)	16.1 (8.8)	16.8 (8.1)	0.647
Beck Anxiety Inventory[g] (SD)	13.9 (8.8)	14.9 (8.5)	14.4 (9.0)	13.4 (8.5)	0.547
Use of ADHD medication at baseline[h], No. (%)	5 (4.2)	3 (5.5)	4 (6.7)	1 (1.7)	0.177
ToL: accuracy	118.3 (20.4) (n = 101)	107.4 (18.0) (n = 46)	118.2 (21.3) (n = 51)	118.5 (19.7) (n = 50)	0.948
ToL: reaction time	14385.4 (4122.4) (n = 101)	12863.5 (4060.5) (n = 46)	14602.5 (4246.8) (n = 51)	14163.9 (4022.3) (n = 50)	0.595
Stroop: interference	95.8 (141.6)	95.6 (118.8) (n = 53)	72.6 (105.5)	119.0 (167.0)	0.075
Stroop: accuracy congruent trials	0.98 (0.02)	0.97 (0.04) (n = 53)	0.98 (0.03)	0.99 (0.02)	0.044
Stroop: accuracy incongruent trials	0.94 (0.17)	0.93 (0.15) (n = 53)	0.96 (0.13)	0.93 (0.20)	0.403
BART: Adjusted Average Pumps	36.6 (12.2) (n = 118)	33.2 (12.2) (n = 54)	36.6 (13.0) (n = 59)	36.6 (11.5)	0.993

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 patients in CBT/Integrated and CBT/SUD (*t*-test or Chi-square tests).

[b] Highest completed education level: low (primary school); average (lower general secondary education); higher (vocational education/higher general secondary education or pre-university education); highest (higher vocational education/academic education).

[c] 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.

[d] At randomization.

[e,f,g] Higher scores indicate more severe symptoms.

[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.

pump, money (5 cents) was accumulated in a temporary bank, but when the balloon exploded, all money in the temporary bank was lost. Twenty balloons were presented and for each balloon the participant had to decide when to stop pumping and collect the money from the temporary bank into the permanent bank. Each balloon had the probability to explode between 1 and 128 pumps with an average breakpoint of 64 pumps; participants were simply informed that the balloon could break anywhere from the first pump all the way through enough pumps to make the balloon fill the screen. Participants were asked to try and earn as much money as possible and were informed that the money would not really be paid. The measure that we used from this task was the average number of pumps used only on balloon trials that were banked, excluding those balloons that exploded (Lejuez et al., 2002).

2.5.3. Outcome variables

Phase I drop-out (treatment session 1–4, before randomization) and treatment outcomes (ADHD symptom severity and alcohol/drug use according to the TLFB at post-treatment and follow-up) were used as dependent variables for the various research questions.

2.6. Data analysis

Between-group (experimental versus control) differences in baseline characteristics were analyzed using Chi-square tests for dichotomous variables and independent t-tests for continuous variables. The continuous variables age, depression symptoms and anxiety symptoms have been mean centered before analysis.

For the first research question, addressing the prediction of phase I drop-out, we used univariate logistic regression analyses; predictors were regressed one by one on the drop-out variable. Predictors that were significantly associated with drop-out ($p < .10$) were also included in a multiple logistic regression model, which included all variables simultaneously. For these analyses, a total of 174 patients were available, including 55 patients that dropped out in the allocated time frame.

For the second research question, addressing the prediction of outcomes in CBT/Integrated (n = 60), we used Generalized Linear

Mixed Model regression analysis (GLMM). To model baseline variance in the GLMM, we fitted a random intercept model in which the scores on the outcome measures at end of treatment and follow-up were used as the dependent variable. The predictors were included in the model one by one; for each predictor a separate model was specified using the R package lme4 [https://cran.r-project.org/web/packages/lme4/citation.html]. In this analysis, no distinction could be made between the outcome at post-treatment and 2-month follow-up.

Finally, GLMM was also used to explore patient-treatment matching. In these analyses, both patients randomized to CBT/Integrated and patients randomized to CBT/SUD were included (n = 119). The predictors, condition, and predictor X condition terms were added to the model one by one; for each predictor a separate model was specified using the R package lme4 [https://cran.r-project.org/web/packages/lme4/citation.html].

Analyses were performed with Microsoft R open version 3.4.0; using the package lme4 for the GLMM analyses. Alpha was set at $\alpha = 0.05$, two-sided.

There were missing data at baseline due to logistic reasons on the BART for 2 patients, on the Stroop task for 2 patients and on the ToL task for 27 patients. The ToL was the last task of the assessment; a considerable number of patients wanted to leave before they finished the full test battery. In CBT/Integrated, 48 out of 60 patients participated in the post-treatment assessment, and 39 patients in the follow-up assessment, resulting in 87 observations for the GLMM analyses on prediction of outcome/follow-up. In CBT/SUD, 46 out of 59 patients participated in the post-treatment assessment and 39 in the follow-up assessment, resulting in a total of 172 observations for patient treatment matching analyses.

3. Results

3.1. Baseline characteristics

Table 1 shows the baseline demographic, clinical and neurocognitive characteristics of the participants. A total of 119 patients were randomized to either CBT/Integrated (n = 60) or CBT/SUD (n = 59). Fifty-five of the 174 eligible patients dropped out of treatment before randomization took place.

3.2. Prediction of phase I drop-out

Table 2 shows that the following predictors were associated with fewer early drop-outs ($p < 0.10$): higher level of education, being employed, alcohol as only SUD, higher accuracy and reaction time score on the ToL, higher accuracy on congruent trials in de Stroop task, and higher scores on the BART. In the multivariate model in which these variables were included, only type of SUD (OR = 15.99, C.I. = 2.73–315.75, p = .012) and accuracy on the ToL (OR = 0.98, C.I. = 0.95–1.00, p = .045) remained as significant ($p < 0.05$) independent predictors.

3.3. Prediction of outcome in CBT/Integrated

3.3.1. Prediction of ADHD symptoms

More baseline depressive symptoms and anxiety symptoms were significantly associated with more ADHD symptoms at post-treatment /follow-up ($p < .001$). The use of ADHD medication at baseline was also significantly associated with more ADHD symptoms at post-treatment/follow-up (p = .003) (see Table 3).

3.3.2. Prediction of substance use

Only accuracy on the ToL was significantly associated with substance use at post-treatment/ follow-up, with lower accuracy scores related to lower substance use at outcome ($p < .001$) (see Table 3).

Table 2
Predictors of early drop-out from cognitive behavioral treatment: results of univariate regression analyses.

	Odds Ratio	Confidence Interval	p-value
Age	0.98	0.94–1.01	0.218
Gender (women, with men as reference)	0.00	N.A.	0.997
Married/ cohabitant (yes versus no)	0.79	0.40–1.55	0.505
Job status (employed vs unemployed)	0.52	0.25–1.07	0.074
Education level[a] (low as reference)			
Average	0.66	0.27–1.66	0.376
Higher	0.33	0.13–0.85	0.022
Highest	0.07	0.00–0.40	0.014
Primary substance of abuse (other substance, with alcohol only as reference)	9.34	2.67–59.12	0.003
Substance use severity[b] (past week)	1.13	1.01–1.27	0.039
ADHD rating scale	0.97	0.92–1.01	0.176
Beck Depression Inventory	1.00	0.96–1.04	0.928
Beck Anxiety Inventory	1.01	0.98–1.05	0.473
Use of ADHD medication (yes versus no)	1.32	0.26–5.57	0.715
ToL: accuracy	0.97	0.95–0.99	0.003
ToL: reaction time	1.00	0.9998–1.0000	0.041
Stroop: interference	1.00	1.00–1.00	0.992
Stroop: accuracy congruent trials	0.00	0.000–0.053	0.021
Stroop: accuracy incongruent trials	0.67	0.10–5.53	0.681
BART: Adj Avg Pumps	0.98	0.95–1.00	0.091

Abbreviations: SUD: Substance Use Disorder; ADHD: Attention Deficit Hyperactivity Disorder ToL: Tower of London; BART: Balloon Analogue Risk Task.

[a] Highest completed education level: low (primary school); average (lower general secondary education); higher (vocational education/higher general secondary education or pre- university education); highest (higher vocational education/academic education).

[b] Excessive use, 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.

3.4. Patient-treatment matching

No significant predictor by treatment interactions were found, neither for ADHD nor SUD outcomes (results not shown). This means that there were no patient characteristics predicting a clear benefit of CBT/Integrated over CBT/SUD or vice versa.

4. Discussion

This study examined the role of different patient factors (socio-demographic factors, clinical characteristics and cognitive functioning) as predictors of early drop-out from CBT treatment, as predictors of treatment outcome in CBT/Integrated, and as candidates for patient-treatment matching to either CBT/Integrated or CBT/SUD.

The results indicated that a lower level of education, unemployment, drug use disorder (vs alcohol use disorder), substance use severity, lower accuracy and shorter reactions times on the ToL, lower accuracy on congruent trials of the Stroop, and a lower BART score were associated with higher drop-out from CBT treatment in Phase I ($p < .10$). Type of SUD (drugs vs alcohol) and accuracy on the ToL however were the only independent predictors in the multivariate model. This means that for a patient with a drug use disorder the odds of dropping out of treatment are 9 times higher than for a patient with an alcohol use disorder, and for a single point higher result on accuracy of the ToL, the chance of dropping out is 3% lower, according to the results of the bivariate analyses. Our finding regarding the ToL is in line with many other studies demonstrating that impaired cognitive functioning is a predictor of early drop-out from addiction treatment (Dominguez-Salas et al., 2016). Our results on the distinction between

Table 3
Predictors of ADHD and SUD symptom severity outcome in CBT/Integrated: results from Generalized Linear Mixed Models.

	ADHD symptoms outcome		Substance use severity outcome	
	Beta	P value	Beta	P value
Age	0.11	0.413	−0.21	0.364
Gender (women, with men as reference)	0.05	0.737	0.16	0.426
Married/ cohabitant (yes versus no)	0.07	0.615	−0.00	0.974
Job status (employed vs unemployed)	−0.10	0.482	−0.16	0.195
Education level (low as reference)				
Average	0.20	0.367	0.47	0.199
Higher	0.20	0.366	0.38	0.328
Highest	0.05	0.802	0.37	0.215
Primary substance of abuse (other substance, with alcohol only as reference)	0.03	0.845	−0.08	0.710
Substance use severity[a] past week	−0.01	0.958	N.A.	N.A.
ADHD subtype (inattentive as reference)				
Hyperactive/impulsive	0.12	0.382	0.04	0.815
Combined	0.14	0.329	−0.31	0.123
ADHD rating scale	N.A.	N.A.	−0.21	0.086
Beck Depression Inventory	0.38	< 0.001	−0.10	0.544
Beck Anxiety Inventory	0.46	< 0.001	0.19	0.303
Use of ADHD medication (yes versus no)	0.35	0.003	−4.11	1.00
ToL: accuracy	−0.03	0.837	0.14	< 0.001
ToL: reaction time	−0.07	0.644	N.A.[b]	N.A.[b]
Stroop: interference	−0.01	0.954	0.12	0.581
Stroop: accuracy congruent trials	−0.03	0.801	0.25	0.261
Stroop: accuracy incongruent trials	0.00	0.998	−0.12	0.517
BART: Adj Avg Pumps	0.06	0.668	−0.11	0.559

Abbreviations: SUD: Substance Use Disorder; ADHD: Attention Deficit Hyperactivity Disorder ToL: Tower of London; BART: Balloon Analogue Risk Task.
For each reported Beta in the table, a separate model has been fitted.

[a] excessive use, 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.

[b] ToL reaction time was not included in these analysis because of convergence problems.

alcohol and drug use disorder are consistent with the results of a recent meta-analysis which found higher drop-out rates for studies targeting cocaine, methamphetamines and major stimulants compared with alcohol (Lappan, Brown, & Hendricks, 2019). We found no association between the results on the Stroop task and treatment drop out, in contrast to two other studies, in which a modest association between Stroop effect and SUD treatment retention was found (Brewer et al., 2008; Fagan et al., 2015). Possibly, in this group of SUD patients with comorbid ADHD, inattention and thus interference problems were present to some extent in all participants and had no discriminative value.

With regard to the prediction of treatment outcome in CBT/Integrated, we found that fewer baseline depression and anxiety symptoms and not using ADHD medication at baseline predicted lower ADHD scores at outcome. Possibly, the severity of ADHD symptoms was higher in medicated patients from baseline on, which could explain the positive association at outcome. This also holds for comorbid depressive and anxiety symptoms, which may have been highest in patients with severe ADHD symptoms. Only lower accuracy scores on the baseline ToL predicted lower substance use scores at outcome. We do not have a clear explanation for this counterintuitive finding, which is also inconsistent with our finding that lower accuracy on the ToL predicted higher early drop-out, but one could hypothesize that the relation is confounded by a third variable, such as motivation (which we did not measure). Patients with a low ToL score who were nevertheless retained in treatment, scored high on motivation to change their substance use behavior, which is in turn linked to treatment outcome (DiClemente, Corno, Graydon, Wiprovnick, & Knoblach, 2017).

Finally, we demonstrated that no patient characteristics were associated with a benefit of CBT/Integrated over CBT/SUD or vice versa, meaning that the benefit of CBT/Integrated is not limited to a specific subgroup of SUD patients with ADHD.

This was the first study to explore potential predictors for drop-out, outcome and patient-treatment matching in CBT/Integrated, but also in psychotherapies in adult SUD patients with ADHD in general. Quite a large number of patients participated in this study, and information was collected on a large range of potential relevant factors.

However, the study also has some limitations. First, although a variety of patient-related predictors were included, other patient-related or treatment-process predictors could not be tested. As pointed out by Brorson et al. (2013), treatment factors such as treatment setting and duration and treatment process factors such as treatment alliance may also be of high relevance for drop-out and deserve more attention in future research. Second, since abstinence was not required in this study, participants might have been (mildly) intoxicated with alcohol or drugs during the assessments, which could have influenced the results of the cognitive tasks in particular. Furthermore, we administered the diagnostic assessment of ADHD during active substance use and during abstinence and found very similar results (van Emmerik-van Oortmerssen et al., 2017). Third, we did not correct for multiple testing because of insufficient sample size; this could have induced Type I errors. Fourth, the current study did not provide tangible rewards for the BART performance, which might have influenced the results. Lastly, the effect size of the treatment results we found in the RCT were modest, suggesting that further improvement in the treatment of this complex comorbid patient group is still needed.

Our findings are of direct clinical relevance. As many patients drop out from addiction treatment in an early phase, and predictors for drop-out are known, patients who are at risk for early drop-out should be identified by a screening procedure and offered alternative or additional interventions. More specifically, this includes interventions that do not require as much of the attention, memory, and planning functions as traditional therapies. Contingency management, for instance, has lower drop-out rates than traditional treatments (Petry, Martin, Cooney, & Kranzler, 2000) and could be used in combination with traditional therapy. Furthermore, several interventions to improve neurocognitive functioning have been designed and although research on this topic is limited, positive results also on treatment outcomes have been reported (Bates, Buckman, & Nguyen, 2013). More research on alternative interventions to enhance treatment retention is paramount.

Finally, our finding that the benefit of CBT/Integrated was not restricted to a specific subgroup of patients, allows for a broader dissemination of this treatment for SUD patients with comorbid ADHD.

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6. Contributors

Authors RAS, WvdB, EV, AG and KvE designed the study and wrote the protocol. FK coordinated data collection. MB conducted the statistical analysis. KvE wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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