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ORIGINAL RESEARCH

A Prospective Biopsychosocial Repeated Measures Study of Stress and Dropout from Substance Addiction Treatment

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Introduction: This prospective, repeated-measures observational study tested biopsychosocial variables as risk factors for dropping out of inpatient substance addiction treatment. Substance use disorder (SUD) is viewed as a chronic relapsing disease caused by an interaction between biological, psychological, and social factors. However, there is a lack of prospective studies that combine biopsychosocial variables when assessing dropout. The aims of this study were to investigate whether there was 1) An association between biopsychosocial factors and dropping out of inpatient substance addiction treatment, 2) An interaction with SUD diagnosis and cortisol, and 3) Different dropout rates between short-term and long-term institutions.

Materials and Methods: Patients (n = 173) were recruited from two inpatient treatment centers in Norway between 2018 and 2021. The following biopsychosocial variables were measured at four timepoints: ward atmosphere (Ward Atmosphere Scale, WAS), psychological distress (Hopkins Symptom Checklist 10, HSCL-10), motivation (M-scale of the Circumstances, Motivation, Readiness, and Suitability questionnaire), and concentration of salivary cortisol (CORT- nmol/L). Cortisol levels were measured for two consecutive days at each timepoint and calculated by two cortisol indices, daytime cortisol slope (DCS) and area under the curve with respect to the ground (AUC_G). A multivariate logistic regression analysis was performed to find an association between dropout rates and the biopsychosocial variables.

Results: The results suggest a lower dropout odds for patients with high motivation (OR = 0.76, p = 0.022) and patients admitted to short-term treatment (OR = 0.06, p = 0.005). An interaction with stimulant SUD and DCS (OR = 13.74, p = 0.024) also revealed higher dropout odds. No statistical significance was found for psychological distress, WAS, and cortisol AUC_G.

Conclusion: The results support monitoring motivation during treatment and further investigating biopsychosocial variables when assessing dropout risk together with SUD diagnosis.

Keywords: cortisol, psychological distress, ward atmosphere, retention, drug abstinence

Introduction

Retention and completion of SUD -programs are associated with positive treatment outcomes.[1,2] A Norwegian study of treatment effect in five residential treatment facilities found that relapse occurred among 37% of the sample three-month after submission.[2] Studies of patients receiving treatment in therapeutic community-based programs have shown significant improvements, including 50% reduction in prevalence of weekly or daily cocaine use at 5 years follow up compared to the year before entering treatment.[3] Even though systematic reviews show reduction in substance abuse during treatment, the effect on a longer time perspective is unclear.[1,4] Meta-analyses of Cognitive Behavioral Therapy (CBT) based treatment of SUD have also revealed significant effects in terms of quantity and frequency of alcohol and drug use.[5] Compared to untreated or minimally treated control groups, CBT had up to 26% better outcomes.[5,6] Research

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on the important association between successful prison addiction programs and desistance from crime has also been found.[7,8]

Dropping out of substance addiction treatment is considered a major challenge in the field of substance addiction research.[2,9] Studies have tried to identify the risk factors of dropout, but the only consistent risk factor that they have identified is being a younger age.[10–18] Research on dropout has primarily focused on pre-treatment factors, such as demographic and patient-related factors.[17,19] Instruments for monitoring individual treatment processes have been developed over the past several decades, and one of the reported benefits of using these tools for monitoring is reduced dropout.[20–22] However, we lack empirical evidence that proves these systems can predict dropout.[19] Dropout rates are still relatively high, and studies that focus on factors that can be assessed during treatment while investigating risk factors for dropout are necessary.[10,11,13,17,19]

Although several studies have investigated individual factors connected to dropout from substance addiction treatment, the literature is dispersed across various disciplines and foci. This study seeks to bridge the gap in research by examining how multiple factors affect the odds of dropping out of treatment. Specifically, we draw upon the biopsychosocial model of addiction, which views substance addiction as a chronic relapsing disease caused by an interaction between biological, social, and psychological factors.[23–26] Developments that have been made in the SUD research field over the past few decades have provided a growing body of evidence that shows biological factors, such as cortisol, predict dropout from substance addiction treatment.[9,27,28] Psychosocial variables, such as psychological distress and perceptions of the therapeutic milieu, have also been linked to dropout.[29] However, few studies use the biopsychosocial model when assessing dropout risk.

Abnormal cortisol levels have been found to be associated with mental disorders, and normalization of secretion patterns are important for recovery.[30] Salivary cortisol is released in response to stress and is viewed as a possible marker that an individual is vulnerable to substance addiction and relapse.[31–35] There is also assumed to be a reciprocal relationship between cortisol, emotions and behavior that influences vulnerability to addiction and relapse in individuals with SUD.[36,37] However, the results from research on cortisol have provided conflicting results.[9,27,37,38] There is thus a need for prospective studies that take psychosocial variables into account when assessing dropout risk.[37–39]

Studies assessing salivary cortisol in the SUD population have shown disparate results in predicting dropout. Research has shown both higher and lower cortisol levels and HPA-activation in the SUD population.[9,27,40–44] These findings are comparable with studies on HPA-axis functioning in individuals with psychiatric disorders, where both hypo- and hypercortisolism have been associated with aggression, depression, and behavioral issues.[45,46] Findings point to both differences in cortisol response depending on the substance being used and variety in the same SUD group, which could be explained by different study designs, phases of withdrawal, or interacting psychosocial variables.[42,44,47–49] Normalization of cortisol levels during recovery has been reported in both individuals with alcohol dependency[50] and opioid dependency.[51] A limitation of previous research is the lack of repeated measures and a standardized protocol for sampling and calculation of salivary cortisol measures. Of the few prospective studies,[27,38,42,52] a study conducted by Jaremko et al[38] is of special interest due to the fact that it combined biological and psychosocial variables when assessing dropout risk. This study found that abnormal cortisol measures increased dropout risk and elevated psychological distress and poor treatment engagement in those who dropped out.[38]

The relationship between psychological factors and substance addiction is well documented. More than 50% of individuals with a SUD will experience mental health illness during their lifetime.[53,54] The co-occurrence between psychiatric disorders and SUD might be rooted in a shared genetic vulnerability, or it could be that mental illness might be the reason for substance use or vice versa.[55,56] A higher substance use relapse rate has been found in individuals with SUD who also have a co-occurring psychiatric disorder.[57]

Recent research points to psychological factors and psychological distress as important factors in predicting dropout.[16,58–61] Research has found associations between psychological stress and retention through the use of questionnaires that capture stress levels, such as the Symptom of Stress[58] inventory and Hopkins Symptom Checklist.[54,58,59] In a study from 2021,[60] Ormbostad et al investigated whether dropout was a deliberate or impulsive act. They found that patients who dropped out of treatment had high levels of emotional distress and reported difficulty with program-related

factors, such as rules and limit-setting. The treatment-related factors that patients reported as being difficult included group therapy, the work structure, sharing accommodations with other patients, and not having access to clinical staff.[60]

In residential treatment of SUD, the social environment with the other patients and the staff is an important part of the treatment process. Studies point to both the therapeutic alliance[57] and the therapeutic environment[62–64] as important factors for treatment retention. Positive identification and affiliation with the social environment during the first weeks in treatment also seem to be central for retention.[65] The Ward Atmosphere Scale (WAS[65]) is a questionnaire developed to capture perceptions of the therapeutic environment at inpatient clinics. The WAS has been useful in predicting retention in mental health settings,[62] and it has been found that patients who report less favorable perceptions of the ward atmosphere have a higher dropout risk.[66,67] Lower levels of perceived support from staff predicted dropout from substance addiction treatment in a study from 2006,[68] and Carr et al[62] found that heightened perceptions of orderliness (one of the domains in WAS) predicted retention in a therapeutic community residential clinic for substance addiction. Another study found that patients who were considered to be at high risk of dropping out seemed to profit in a therapeutic environment characterized by a high degree of support but low control.[68] Satisfaction with treatment has also been shown to be positively associated with treatment completion.[68,69] Patients who report lower levels of satisfaction have been found to be 2.5 times more likely to drop out.[69] This is in line with the Risk-Need-Responsivity model, and especially the matching concept where the patient's social and psychological needs are determinants of which program the patient should attend.[70] Furthermore, matching seems important for treatment outcome. For instance, Stallvik et al[71] found that matching patients with SUD to optimal care level by using the American Society of Addiction Medicine (ASAM) - criteria significantly reduced alcohol and cannabis use after 3 months in treatment. ASAM is based on measure of addiction severity, as well as psychosocial factors. The literature regarding dropout rates and treatment dose seems to be somewhat mixed. Even though it is well established that treatment retention and engagement is associated with positive treatment outcomes,[10,38] studies have found that programs characterized by more and longer treatment sessions have a higher dropout rate.[72]

A lack of proper motivation has often been used to explain why individuals fail to attend or complete treatment for substance addiction,[73] and higher motivation has been found to be significant in predicting treatment retention.[16,40,74,75] In a four-scale instrument called Circumstances, Readiness for Treatment, and Suitability for the Treatment Program (CMRS), motivation is treated as multidimensional and operationalized. In a study from 1998, Joe et al[76] found that pre-treatment motivation was positively associated with retention for individuals in substance addiction treatment, as the readiness modality was the strongest predictor of retention. In a more recent study, motivation was found to interact with distress tolerance in predicting retention. Higher motivation scores increased the likelihood of retention in individuals with high distress tolerance.[77]

In general, findings from the literature suggest that there could be both biological and psychosocial risk factors for dropping out of substance addiction treatment. However, to the best of our knowledge prospective studies with repeated measures of a combination of biopsychosocial variables seem to be lacking. The present study aims to fill this gap in the literature by prospectively examining the combination of biological, psychological and social predictors of treatment dropout from residential addiction treatment. The development of biopsychosocial factors during the course of treatment may have important clinical implications and could help identify areas for improvement in clinical services.

This study aimed to investigate if there is 1) an association between biopsychosocial factors and dropping out from inpatient substance addiction treatment, 2) an interaction with SUD diagnosis and cortisol, and 3) different dropout rates between short-term and long-term institutions.

Method

Study Design and Setting

This prospective observational study was conducted in a cohort of patients admitted to substance addiction treatment. Two residential units in the middle region of Norway participated in the study. Both units offered inpatient treatment for substance addiction. One was a short-term (2 months) clinic, and the other was long-term (6 months). The number of available treatment beds was 24 (short-term) and 15 (long-term) in 2020. A multidisciplinary treatment is offered in these

units with a combination of individual, group, and milieu therapy. The staff members come from a range of disciplinary backgrounds and consist of social workers, psychologists, psychiatrists, doctors, nurses, physical therapists, and other trained or untrained staff. Patients can also participate in physical activities and training as part of their treatment or in their leisure time. The main goal of the treatment is to improve individual coping and overall functioning, and individual adjustments are tailored if necessary.

The long-term treatment (6 months) also follows a specific treatment structure and philosophy. The long-term clinic is categorized as a modified therapeutic community (TC).[77] The program is organized into 3 steps where the patient takes on more responsibility and is exposed to different roles and interactions with each step. A fundamental element of TS is social learning as the therapy is based on "community as a method". The days are structured with work assessment, daily meetings and group treatment, and the program is meant to facilitate patient interactions with staff and other patients. Taking an active part in their own treatment and the treatment of other patients is considered to be a core concept of the program, as is milieu therapy that targets naturally occurring situations in the clinic.

Recruitment and Study Participants

The only inclusion criteria for participating in the study was admission. Exclusion criteria included being admitted involuntary or only admitted for a shorter period (< 2 months). Patients who were judged to be mentally or physically incapable of giving consent on the day of data collection (assessment by the clinical staff) were also excluded from the study. According to the execution of the sentence act, §12 is considered voluntary treatment, and individuals in this category were asked to participate. The §12 law provides the opportunity for criminal proceedings to take place in an approved inpatient treatment facility for SUD. The treatment centers only offer treatment to people above 18 years old, so all study participants were adults.

Patients were sought out by the first author (K.B.) or one of the research assistants during their first week in treatment and asked to participate in the study. Both oral and written information was given before they signed the form confirming informed consent. Patients could either sign right away or take a few days to think about their decision. Patients who handed in questionnaires for each timepoint received a gift card of 300NOK at the last timepoint as an incentive for participating in the study.

Data were collected consecutively during the treatment stay for each participant, with measures collected every other week for 8 weeks. The first timepoint was in treatment week 2, and the 4th was in treatment week 8. Salivary cortisol, motivation, and psychological distress were measured at each timepoint. The WAS (Ward atmosphere scale) was included at timepoint 2 because the participants could not assess the ward atmosphere before they had experienced it.

Measures

A comprehensive questionnaire was developed for each timepoint (T1-4) and included validated instruments of ward atmosphere, motivation, and psychological distress. A sociodemographic form developed for this study was also used to collect information about background variables (T1). Salivary cortisol was collected at all timepoints (T1-4). The data collection period was from June 2018 to October 2021. Due to the COVID-19 pandemic, data collection was placed on hold from March to September 2020, and procedures for collection of salivary cortisol were adapted according to the Norwegian government's COVID-19 measures.

Dropout

Dropout was defined as discontinuation of the treatment according to the treatment plan. Dropout status (yes/no) was retrieved from the patient record for each timepoint (T1-4).

SUD and Other Diagnoses

Primary SUD and psychiatric diagnoses according to the International Classification of Diseases (ICD-10, World Health Organization[75]) were obtained from the patient record. SUD diagnoses were used as categorical variables, while psychiatric diagnoses were registered with number of diagnoses (number of psychiatric diagnoses).

Sociodemographic Form

The sociodemographic form developed for this study obtained information about age, sex, substance use history, §12 status, and previous inpatient stays. The form was handed out at T1. The form was structured with predefined response options, except for age and years of substance use. Age and years of substance use was assessed and coded in years, and the options for gender were male and female. For §12 status, the answer was either yes or no to the question of whether they were admitted according to §12 now. The patients were also asked how many times they had been admitted to inpatient substance addiction treatment prior to their current stay, with predefined response alternatives.

Cortisol (CORT)

Procedures for sampling and analyzing cortisol were the same as reported in Bohle et al.[52] In short, all sampling was performed over two consecutive days, 4 times a day for each timepoint (T1-4). Samples were gathered using a saliva collection device (Sarstedt Nümbrecht, Germany) that consisted of a cotton swab and a sampling vessel. The samples were analyzed by Department of Medical Biochemistry, Møre, and Romsdal Hospital Trust. Cortisol levels were measured using an immunochemical assay on a Roche Cobas 8000 e801 automated analyzer (Roche Diagnostics, Oslo, Norway). To examine different aspects of HPA axis functioning, the daytime cortisol slope (DCS) and AUC were calculated. DCSs were quantified by calculating the difference between morning and afternoon samples divided by the total time between the two samples.[78] The area under the curve with respect to the ground (AUC_G) was calculated according to the method described by Pruessner et al.[79] The AUC_G is the total AUC of all measurements for each time point based on the mean time of day for each sample time (ST). The formula for AUC_G is summarized as: $AUC_G = \sum i = 1n - 1\left(m_{(i+1)} + m_i\right) \cdot t_i 2$, where t_i denotes the individual time distance between measurements, m_i denotes the individual measurement, and n represents the total number of measures. In line with recommendations before calculating cortisol, concentrations exceeding 2.5 SD from the mean of each sample time (ST) were excluded from the dataset before calculating the AUC_G and DCS.[80–82]

The Ward Atmosphere Scale

The short form consists of 40 items that assess a variety of features of the therapeutic environment, including relationships, involvement, support, personal growth, autonomy, personal problems, anger and aggression, system maintenance, order, and program clarity.[66] The respondent is presented with statements such as "The doctors have little time to cheer up the patients" and "The personnel knows what the patients need" and responds from "3 – Strongly agree" to "0 – Strongly disagree". Internal consistency of the scale was 0.69, 0.71, and 0.72 (Cronbach's alpha) for timepoints 2 to 4.

Motivation

A modified version of the validated motivation scale of the Circumstances, Motivation, Readiness, and Suitability questionnaire[83] (CMRS) was used to measure motivation. The CMRS is designed to measure intrinsic motivation and readiness for treatment and predict retention in treatment among abusers of illicit drugs. This scale presents statements such as "Often I don't like myself because of my drug use" and "I came to this program because I really feel that I`m ready to deal with myself in treatment". The participants are asked to rate these statements from "1 –Disagree" to "4 – Strongly Agree". Internal consistency of the motivation scale for each timepoint 1–4 was 0.81, 0.79, 0.82, and 0.86 (Cronbach's alpha).

Psychological Distress

Hopkins Symptom Checklist-10 (SCL-10)[84] was used as a measure of psychological distress. This study adopted a Norwegian version[85] of the structured self-administered questionnaire, which includes ten items (suddenly scared for no reason, feeling fearful, faintness, dizziness and weakness (one item and three score options), feeling tense, blaming yourself, difficulties with sleep, feeling of worthlessness, feeling blue, feeling hopeless, and feeling everything is an effort) scored on a 4-point Likert scale from 1 (not at all) to 4 (extremely). Scores were summarized and divided by the number of items, giving a total score between 1 and 4. A mean score of 1.85 is considered a valid cut-off to indicate severe psychological distress.[86] The internal consistencies of the SCL-10 were between 0.84 and 0.89 (Cronbach's alpha) for timepoints 1 to 4.

Statistical Analysis

STATA/SE 16.1 was used for the statistical analyses aimed at the research questions. Univariate analyses and descriptive statistics were performed with IBM SPSS Statistics 27. Statistical significance was set at $p < 0.05$. Descriptive statistics for continuous variables are presented with means and SDs. Frequency distributions are presented for categorical variables.

Potential multicollinearity was inspected with variation inflation factor (VIF). VIF-scores were between 1.048 and 2.847, indicating no issues with multicollinearity. Cook's distance was used to check for influential cases, and no outliers were detected (criterion set to 1.00).

Univariate analysis was run to test differences in dropout rates between the two institutions, differences in motivation between the SUD diagnoses, and differences between patients with high HSCL-10 scores (above 1.85). Differences in motivation and the AUC_G for patients admitted to previous inpatient treatment versus patients with few inpatient stays was also tested (> 2 previous inpatient stays: yes/no).

In the final analysis, intermediate and multiple logistic regression was used with dropout as the outcome. Variables included in the final model were a combination of main interest (AUC_G, DCS, SCL-10, WAS, and MOT) and common interest (time, sex, age, institution, SUD diagnosis). Non-significant variables of no particular interest were excluded from the analysis. The final logistic regression model analysis consists of an adjusted logistic regression effect for dropout relative to the change in AUC_G, DCS, Motivation, Ward Atmosphere (WAS), psychological distress (SCL-10), time, sex, institution, and SUD diagnosis. An interaction between SUD diagnosis and cortisol DCS was included in the final model. Models with only the main effects and models with adjustments for the interaction terms were compared. Models with only main effects were tested before the interaction terms were entered into the model. Only the significant interaction terms were included in the final model ($p<0.05$).

Results

Characteristics of the Study Sample

Out of the 196 patients who agreed to participate in the study, 173 were included in the final analysis. Seven participants dropped out of treatment after consent was given and before T1. These patients left the clinic and did not return, and thus no research data were collected from this group. Four others withdrew from the study during the data collection period, and 23 patients were excluded from the data set due to extreme values (2.5 SDs above the mean for each sample time: ST).

The final sample consisted of 129 (74.6%) male and 44 (25.4%) female patients. Age varied from 20 to 69 years, with a mean of 38.94 years (SD = 11.06). The most common SUD diagnosis was alcohol dependence (44.5%, n = 77), and only 5 (2.9%) respondents had the SUD diagnosis of multiple drug use.

Univariate Tests

The univariate analysis revealed a significantly higher age for patients who had been admitted to several (>2) inpatient treatments ($p = 0.024$). At T1, patients admitted to previous inpatient treatment more than 2 times displayed a significantly higher motivation ($p = 0.002$) and a lower AUC_G ($p = 0.020$). A significantly higher motivation at T1 (but not T2-4) was also found in individuals with alcohol dependence vs dependence on illicit drugs ($p = 0.002$) and patients with a HSCL-10 score above the cut-off at 1.85 ($p = 0.023$).

In addition, a chi-square test was run to test for differences in dropout rate between the two institutions, correcting for treatment length. Comparing the dropout rates at week 8 in treatment revealed no significant difference between the two institutions ($p = 0.081$).

Dropout and Biopsychosocial Variables

A total of 43 (24.8%) participants dropped out of treatment during this study. Eight patients dropped out after T1 (2 weeks in treatment). Twelve dropped out after both T2 and T3, and 11 patients dropped out after T4. The long-term

institution had the highest dropout rate, and males dropped out more often than females. Table 1 presents a descriptive comparison of dropouts and treatment completers as well as descriptions for each institution.

A total of 4405 salivary cortisol samples were collected and analyzed in this study. Mean values for each sample time (ST) across the timepoints (T1–T4) were 6.74 nmol/l at ST1 (SD = 3.09, Range: 1.5–21.6), 6.59 nmol/l at ST2 (SD = 3.00, Range: 1.5–16.9), 6.52 nmol/l at ST3 (SD = 2.95, Range: 1.5–16.2), and 6.48 nmol/l at ST4 (SD = 2.91, Range 1.5–23.7). The mean and standard deviation for the cortisol indexes (AUC_G and DCS) for each time point are presented in Table 2, which also shows whether or not patients dropped out.

Main Results

For the unadjusted analysis, the effect of one variable at a time on dropout was assessed (Table 3). The only significant variable in the unadjusted analysis was institution. Patients were 64% less likely to drop out from the short-term treatment program. Sex differences were also close to significance, with a 56% lower odds of dropout among women. Psychiatric diagnoses, years of addiction, and number of times in treatment were not significantly associated with

Table 1 Sample Characteristics and a Descriptive Comparison of the Two Institutions

	Whole Sample	Institution		Dropout	
	Total	Short-Term	Long-Term	Yes	No
Number of subjects, n (%)	173	138 (79.8)	35 (20.2)	43 (24.8)	130 (75.14)
Dropouts, n (%)	43 (24.8)	29 (21)	14 (40)		
Sex					
Male, n (%)	129 (74.5)	101 (73.2)	28 (80)	36 (83.7)	93 (71.5)
Female, n (%)	44 (25.4)	37 (26.8)	7 (20)	7 (16.3)	33 (26.8)
SUD diagnosis n (%)					
Alcohol	77 (44,5)	68 (49.3)	9 (25.7)	20 (46.5)	57 (43.8)
Opioids	18 (10.4)	11 (8)	7 (20)	5 (11.6)	13 (10)
Stimulants	38 (22)	29 (21)	9 (25.7)	11 (25.6)	27 (20.8)
Cannabinoids	24 (13.9)	17 (12.3)	7 (20)	5 (11.6)	19 (14.6)
Sedative hypnotics	8 (4.6)	7 (5.1)	1 (2.9)	1 (2.2)	7 (5.4)
Multiple drug use	5 (2.9)	3 (2.2)	2 (5.7)	1 (2.2)	4 (3.1)

Table 2 Overview of the Development of the Biopsychosocial Variables (AUC_G, DCS, HSCL-10, WAS and MOT) at Each Timepoint Divided into Dropout Yes/No

	Dropout	T1[a]		T2[b]		T3[c]		T4[d]	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
AUC_G	Yes	40	21.1	30.99	14.84	30.08	10.06	33.06	26.99
	No	46.09	22.55	39.76	16.36	37.42	14.72	40.01	21.31
DCS	Yes	1.04	0.75	0.99	0.81	1.03	0.64	1.23	0.8
	No	1.28	0.94	1.19	0.79	1.28	0.86	1.08	0.75
HSCL-10	Yes	2.25	0.79	2.09	0.68	1.95	1.01	2.22	0.70
	No	2.29	0.69	2.06	0.64	2.04	0.70	1.89	0.68
MOT	Yes	17.02	3.06	16.73	3.30	17.27	2.34	18.22	1.78
	No	17.42	3.19	16.99	3.12	17.15	3.32	16.64	3.72
WAS	Yes	–	–	23.96	6.00	25.00	6.36	28.00	6.86
	No	–	–	25.51	4.57	25.84	5.33	25.38	5.37

Notes: [a]T1: Time point 1 during the second treatment week; [b]T2 is in week 4; [c]T3 is in week 6; and [d]T4 is in week 8.
Abbreviations: SD, standard deviation; AUC_G, Area under the curve with respect to ground; DCS, Diurnal cortisol slope; HSCL-10, Hopkins symptom checklist 10; MOT, Motivation; WAS, Ward Atmosphere scale were not included at the first timepoint.

Table 3 Association Between AUC_G or DCS and Dropout Adjusted for Time, Age, Sex, Institution, Number of Psychiatric Diagnoses, Years of Addiction, and SUD Diagnosis. Unadjusted and Adjusted Multiple Regression Analyses

	Unadjusted Effects		P values	Adjusted Effects – Model with Main Effects		P values	Adjusted Effects – Model with Main Effects and Interactions		P values
	OR	95% CI		OR	95% CI		OR	95% CI	
AUC_G	0.98	0.96: 1.00	0.178	0.97	0.94: 1.01	0.132	0.97	0.92: 1.02	0.277
DCS	0.87	0.58: 1.31	0.525	1.19	0.48: 2.93	0.679	0.28	0.06: 1.31	0.107
Motivation	0.99	0.89: 1.10	0.890	**0.82**	**0.67: 0.99**	**0.049**	**0.76**	**0.60: 0.96**	**0.022**
Ward Atmosphere	0.96	0.89: 1.04	0.368	0.99	0.87: 1.12	0.903	0.98	0.85: 1.12	0.781
Psychological distress	0.98	0.94: 1.03	0.601	1.077	0.96: 1.19	0.171	1.09	0.97: 1.23	0.128
HSCL-10 Cutoff	0.67	0.34: 1.32	0.258	–	–	–	–	–	–
Time	–	–	–						0.864
T1	–	–							
T2	–	–	–	0.85	0.17: 4.06	0.843	0.67	0.12: 3.70	0.655
T3	–	–	–	0.78	0.15: 4.03	0.771	0.63	0.11: 3.59	0.608
T4	–	–	–	(Omitted)			(Omitted)		
Age	0.99	0.96: 1.02	0.862	1.05	0.97: 1.14	0.158	1.05	0.97: 1.15	0.191
Sex	–	–							
Male	1.00	–		1.00			1.00		
Female	0.44	0.18: 1.07	0.072	0.43	0.07: 2.41	0.341	0.33	0.05: 2.15	0.250
Institution	–	–							
Long–term	1.00			1.00			1.00		
Short–term	**0.36**	**0.19: 0.69**	**0.002**	**0.13**	**0.02: 0.65**	**0.013**	**0.06**	**0.01: 0.44**	**0.005**
Psychiatric diagnoses	0.99	0.77: 1.28	0.987	–	–	–	–	–	–
Years of addiction	1.02	0.99: 1.05	0.095	–	–	–	–	–	–
Number of treatments	1.09	0.86: 1.39	0.451	–	–	–	–	–	–
SUD diagnosis	–	–	–						
Alcohol	1.00	–		1.00			1.00		
Opioids	1.46	0.55: 3.84	0.439	1.13	0.11: 10.87	0.914	0.17	0.00: 4.65	0.296
Stimulants	1.14	0.51: 2.53	0.743	0.59	0.24: 10.27	0.621	0.09	0.00: 2.44	0.155
Cannabinoids	0.43	0.12: 1.51	0.192	0.50	0.04: 6.10	0.589	0.01	0.00: 8.21	0.202
Sedative Hypnotics	0.42	0.05: 3.27	0.410	1.34	0.11: 15.51	0.810	0.10	0.00: 22.99	0.412
Multiple drug use	1.95	0.40: 9.28	0.401	3.66	0.20: 66.38	0.380	0.16	0.00: 1501.7	0.702

Note: Significant findings are highlighted in bold.
Abbreviations: OR, Odds Ratio; CI, Confidence interval; AUC_G, Area under the curve with respect to ground; DCS, Diurnal cortisol slope; HSCL–10, Hopkins symptom checklist −10; T1–T4, Timepoint 1 to 4.

dropout and were therefore excluded from further analysis. However, the other non-significant variables were included in further analysis due to the fact that they were main explanatory variables or of general interest to our study.

The adjusted analysis tested the effect of the explanatory variables (AUC_G, DCS, motivation, WAS, and psychological distress) on dropout, adjusting for time, age, sex, institution, and SUD diagnosis. This analysis showed a significant association between motivation and drop-out, where every one unit-increase (the scale ranging from 5 to 20) in motivation decreased dropout risk by 1%.

The results also demonstrated a significant effect for a contextual variable: type of institution. Being admitted to short-term treatment reduced the risk of dropping out by 87%, adjusting for the other variables in the model.

In the final multivariate logistic regression analysis (Table 3), we analyzed the association between the explanatory variables (AUC_G, DCS, motivation, WAS, and psychological distress) and dropout, which was adjusted for time, sex, age, institution, and SUD diagnosis. The interaction between SUD diagnosis and DCS was also included in this model (Table 4). The analysis revealed a significant main effect between motivation, institution, and dropout. The main effect for motivation demonstrated that the odds of dropout decreased by 24% for each unit increase in motivation. With respect

Table 4 Extension of Table 3 Results for the Interaction Between SUD Diagnosis and Cortisol DCS

Interaction	OR	95% CI	P values
SUD diagnosis # DCS			0.754
Alcohol	1.00		
Opioids	5.97	0.43: 82.54	0.181
Stimulants	**13.74**	**1.40: 134.64**	**0.024**
Cannabinoids	14.81	0.37: 593.22	0.152
Sedative hypnotics	8.95	0.40: 198.23	0.165
Multiple drug use	12.33	0.01: 29,527.51	0.439

Note: Significant findings highlighted in bold.
Abbreviations: OR, Odds Ratio; CI, Confidence interval.

to the type of institution, being admitted to short-term treatment decreased the dropout odds by 87% when adjusted for the other variables in the model. The interaction between DCS and SUD diagnosis as a whole was not significant, but there was a significant difference between individuals suffering from alcohol dependence versus stimulants. The results showed an increased odds of dropout by 13.74 times for individuals with dependence of stimulants compared to alcohol, dependent on the DCS.

Discussion

In this prospective naturalistic study, the association between biopsychosocial measures and dropout was investigated. According to the biopsychosocial model of addiction, several dimensions, from the molecular to the social level, affect SUD.[25,26] Findings from a multiple logistic regression analysis revealed a significant association between motivation and dropout, but not for the other biopsychosocial variables (HSCL-10, CORT, and WAS). In the final logistic regression model, higher motivation was found to lower dropout odds by 24% per one-unit increase in motivation.

Motivation had a significant ($p < 0.05$) association with dropout in both the adjusted, and the final logistic regression model. The minimum score on the motivation scale is 5, representing low treatment motivation, and highest possible score is 20. Table 2, which presents the development of the explanatory variables through all timepoints, reveals that the mean motivation score is quite high for both groups at the first timepoint, above 17 for both dropouts and treatment completers. This is consistent with previous findings, where pre-treatment motivation has been found to predict dropout from substance addiction treatment.[74–76] Studies investigating motivational interviewing (MI) as a way to enhance participation and retention in substance addiction treatment have shown dispersed results,[86–88] but it has been argued that MI is better than no intervention.[89] Broome et al[90] found that an important factor for motivation were support of significant others. Further research on biopsychosocial factors and dropout should therefore include social networks outside the clinic. Haviv and Hasisi,[7] comparing different prison addiction treatment programs, argue that motivation itself cannot explain decreased recidivism rates. They argue that only an interaction between high motivation and a good treatment program could produce ideal outcomes. In the present study, both treatment length and the Ward atmosphere was controlled for, but future studies could put more emphasis on type of treatment factors as Haviv and Hasisi did.

The results show an increased risk of dropout by almost 14 times for individuals with stimulant dependence, compared to dependence of alcohol, depending on the DCS. This indicates a lower DCS (ie, a flatter curve) in patients with alcohol dependence than in patients with stimulant dependency. Previous findings comparing people with SUD with healthy controls testify to a flattened cortisol curve in patients with alcohol dependency,[48,61] but this does not seem to heighten the dropout risk in our sample. In our sample, the steeper curve in patients with stimulant addiction is associated with dropping out of treatment. As there are few studies investigating basal cortisol levels in stimulant dependent individuals, these findings are difficult to interpret. However, the effect of cocaine on the HPA-axis has been well-demonstrated, and individuals with cocaine dependence have been shown to display higher levels of cortisol when the drug is administered.[91] Elevated levels of basal cortisol have been found in non-abstinent cocaine dependent individuals,[92] and increased morning levels of cortisol have been found to be associated with retention in crack cocaine

users.[9] The effect of amphetamines on the HPA-axis and cortisol levels seems to be more complicated, and more research is needed.[93] The DCS represents the curve from morning to afternoon in our sample, where a higher DCS value represents a larger decline in cortisol during the day. The higher the morning values, the higher the DCS value. This association could therefore be comparable to the elevated morning cortisol in individuals with cocaine addiction[9] even if the study protocol is not similar. Chronic stimulant use is known to increase stress reactivity in abstinent rats and humans,[94] and the steeper DCS in patients addicted to stimulants might thus influence the risk of stress-induced relapse. The results for stimulant dependent individuals in our sample could be in line with previous studies suggesting a dysregulation of the HPA axis in individuals with SUD.[9,95,96]

Looking at the univariate statistics reveals that patients going through treatment for the 3rd or 4th time both have a higher motivation and a lower AUC_G. A higher level of motivation is also found in individuals with severe psychological distress and those with a SUD of alcohol dependence. The significant association between age and several treatments could also have a connection with the severity of substance use history or how many years they have been using substances. The group of patients with several previous inpatient stays also have a significantly lower AUC_G, which is interesting. As previously mentioned, the results for basal cortisol levels in individuals with SUD have been inconsistent, but one could maybe theorize that a more severe substance use history could have a more severe effect on the HPA-axis and hence the cortisol levels.

Several reasons could exist that explain the higher level of motivation in individuals who were admitted to treatment before. It might be that previous inpatient stays and the experience with the demands that it entails could help individuals feel more prepared. The significant association between severe psychological distress and motivation is also interesting because psychological distress did not have a significant effect on dropout. In the case of high motivation in individuals with a score above 1.85 on the HSCL-10, high psychological burden could be a source of motivation. Patients suffering from a high symptom load of psychological distress might be motivated to get treatment in order to find some sort of symptom relief, but it could also be that the motivation itself could produce the stress. Andersson et al's 2018 study also used both the HSCL-10 and the M-scale from the CMRS.[16] They found that higher psychological distress and higher motivation predicted dropout. Another study investigated the role of motivation and distress tolerance for retention and found a significant interaction between high motivation and high distress tolerance in predicting retention.[40] Because there are few studies that investigate the combined role of motivation and psychological distress,[16] future research may want to address this association and include distress tolerance in their investigations.

We did not find a significant association between dropout and psychological distress or perceived ward atmosphere (WAS) in this study. The WAS might not have been significant because it could have just not been an important risk factor. Another explanation could be that the sample came from two different institutions with different treatment lengths and structures. Table 2 displays the mean scores for WAS for both dropouts and treatment completers for each timepoint. The highest possible WAS score is 40, where the mean for the treatment completers is stable at around 25 across all timepoints. The mean for the dropouts varies between below and over 25, but this is probably due to the fact that the number of participants was not stable over the timepoints since some dropped out. Psychological distress was high and similar for dropouts and treatment completers. This tells us that both groups have severe psychological distress, taking the cut-off at 1.85 into account. This aligns with previous findings for the patient group, both for the SCL-10 and for the general co-occurrence of mental disorders in the SUD population.[29,97–99] The non-significance in predicting dropout could be due to properties of the HSCL-10. It could be that the measure is not specific or detailed enough to use in the field of substance addiction. However, previous research has found associations between psychological distress and dropout,[16] so the explanation could also be related to our specific sample rather than the HSCL-10.

Furthermore, the number of psychiatric disorders did not predict dropout. The same was the case for years of addiction and number of times in treatment. A possible explanation for this might be that having many co-occurring psychiatric diagnoses and going through treatment for the 3rd or 4th time could possibly make both the individual and their therapist aware of the situation, which might lead them to individualize treatment as necessary.

The results showed a significant difference between the institutions, where being admitted to long-term treatment gives a higher risk of dropping out of treatment. However, this finding should be interpreted with caution due to the difference in treatment length. To check for this issue, a univariate test comparing the dropout rate in week 8 of treatment

revealed no significant difference in dropout rates between short-term and long-term treatment. This could indicate that the higher dropout risk at the long-term clinic is due to longer "time at risk".

Strengths and Limitations

Strengths

This study has several strengths. First, the prospective design allowed for repeated measures, giving important information about how biopsychosocial factors develops during treatment. Second, the use of both biological and self-reported measures allowed for testing a biopsychosocial model, which is scarce in research on drop-out in substance misuse services. Third, the measuring of cortisol over two consecutive days with 4 samples each day in addition to the use of two different cortisol indices is a strength. These actions were taken to minimize the effect of blunted cortisol activity and random values and provide reliable and valid test samples if a patient missed one or more sample appointments. Fourth, we compared explanatory variables for dropout between short-time and medium-time services.

Limitations

Though this is not necessarily a limitation, we wanted to address the use of a dichotomous outcome variable (dropout: yes/no) and the choice of logistic regression for data analysis. With a continuous variable (days in treatment), a Cox regression survival analysis could be an alternative. However, the exact number of days in treatment was not possible to determine; hence, a logistic regression was the best fit for our data.

There are several limitations connected to the salivary cortisol sampling protocol. First, we did not control for waking time and thus cannot be sure of avoiding the cortisol awakening response (CAR). Second, the use of caffeine or nicotine prior to sampling was not controlled for in the statistical analysis. Instead, we inspected all samples for unusual values, and samples exceeding 2.5 standard deviations from the mean of each sample time were excluded from the data set and further analysis.

The number and timing of timepoints could also be a limitation. The first timepoint was performed in the second treatment week, and the following timepoints occurred every other week until the 8th treatment week. Collecting the first measurement earlier, in the first treatment week, could probably give more information and a more reliable baseline. This would also give a higher participation rate since the patients who dropped out before the first measurement could not participate in the study. Collecting the first measurement on the first treatment day could also provide important information about these early dropouts, who we now know little about.

We did not collect information about cravings in this study. As previous studies have found an association between cravings and retention, this is something we could have monitored. Since psychological distress was not significantly associated with dropout, it would have been interesting to see if there is an association between cravings and dropout, as cravings could produce stress and possibly affect motivation.

Conclusion

In conclusion, our results suggest an association between motivation, sex, and treatment length and an interaction between cortisol DCS and stimulant dependency in predicting dropout. There were no significant results for psychological distress or ward atmosphere in predicting dropout. The results could indicate that different HPA reactivity is dependent on the substances used and that being motivated to participate in treatment is important. The univariate analysis also reveals interesting associations between motivation and times in treatment, psychological distress, cortisol levels, and suffering from alcohol dependence. Assessment of motivation and cortisol during treatment could inform clinicians of the need to tailor interventions toward stress regulation and enhancing motivation in order to increase retention. Future studies may want to monitor other possible risk factors of dropping out of treatment, and the use of a stricter sampling protocol for salivary cortisol is also recommended.

In summary, and as expected, no breakthrough regarding biopsychosocial model for dropout was discovered in this study. Nevertheless, our research represents a small step towards developing this important field of clinical research.

Ethics

The authors have provided the publisher with confirmation that they complied with the legal and ethical obligations. The Regional Committee for Medical Research Ethics in Central Norway approved this study in January 2018 (approval #2017/2057/REK-Midt). We confirm that the study complies with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, or analysis and interpretation of data. Further, all authors participated in drafting, revising and critically reviewing the article, and all gave final approval of the version to be published. All authors have agreed on the choice of journal to which the article has been submitted and agree to be held accountable for all aspects of the work.

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Disclosure

All authors declare that they have no conflicts of interest.

References

1. Malivert M, Fatséas M, Denis C, Langlois E, Auriacombe M. Effectiveness of therapeutic communities: a systematic review. *Eur Addict Res*. 2012;18(1):1–11. doi:10.1159/000331007
2. Andersson HW, Wenaas M, Nordfjærn T. Relapse after inpatient substance use treatment: a prospective cohort study among users of illicit substances. *Addict Behav*. 2019;90:222–228. doi:10.1016/j.addbeh.2018.11.008
3. Hubbard RL, Craddock SG, Anderson J. Overview of 5-year followup outcomes in the drug abuse treatment outcome studies (DATOS). *J Subst Abuse Treat*. 2003;25(3):125–134. doi:10.1016/S0740-5472(03)00130-2
4. Magor-Blatch L, Bhullar N, Thomson B, Thorsteinsson E. A systematic review of studies examining effectiveness of therapeutic communities. *Ther Communities*. 2014;35(4):168–184. doi:10.1108/TC-07-2013-0024/FULL/XML
5. Magill M, Ray LA. Cognitive-behavioral treatment with adult alcohol ad illicit drug users: a meta-analysis of randomized controlled trials*. *J Stud Alcohol Drugs*. 2009;70(4):516–527. doi:10.15288/jsad.2009.70.516
6. McHugh RK, Hearon BA, Otto MW. Cognitive-behavioral therapy for substance use disorders. *Psychiatr Clin North Am*. 2010;33(3):511. doi:10.1016/j.psc.2010.04.012
7. Haviv N, Hasisi B. Prison addiction program and the role of integrative treatment and program completion on recidivism. *Int J Offender Ther Comp Criminol*. 2019;63:15–16. doi:10.1177/0306624X19871650
8. Shoham E, Efodi R, Haviv N, Gross Shader C. Dropout from treatment and desistance from crime among released prisoners in Jerusalem halfway house for prisoners with substance misuse disorder. *Int J Offender Ther Comp Criminol*. 2022;66(10–11):1109–1133. doi:10.1177/0306624X211010291
9. Ligabue KP, Schuch JB, Scherer JN, et al. Increased cortisol levels are associated with low treatment retention in crack cocaine users. *Addict Behav*. 2020;103:106260. doi:10.1016/J.ADDBEH.2019.106260
10. Stark MJ. Dropping out of substance abuse treatment: a clinically oriented review. *Clin Psychol Rev*. 1992;12(1):93–116. doi:10.1016/0272-7358(92)90092-M
11. López-Goñi JJ, Fernández-Montalvo J, Arteaga A. Addiction treatment dropout: exploring patients' characteristics. *Am J Addict*. 2012;21(1):78–85. doi:10.1111/j.1521-0391.2011.00188.x
12. López-goñi JJ, Fernández- Montalvo J, Illescas C, Landa N, Lorea I. Determining socio-demographic predictors of treatment dropout: results in a therapeutic community. *Int J Soc Welf*. 2008;17(4):374–378. doi:10.1111/j.1468-2397.2008.00584.x

13. Li X, Sun H, Puri A, Marsh DC, Anis AH. Factors associated with pretreatment and treatment dropouts among clients admitted to medical withdrawal management. *J Addict Dis*. 2007;26(3):77–85. doi:10.1300/J069v26n03_08
14. Baekeland F, Lundwall L. Dropping out of treatment: a critical review. *Psychol Bull*. 1975;82(5):738–783. doi:10.1037/h0077132
15. Darke S, Campbell G, Popple G. Retention, early dropout and treatment completion among therapeutic community admissions. *Drug Alcohol Rev*. 2012;31(1):64–71. doi:10.1111/j.1465-3362.2011.00298.x
16. Andersson HW, Steinsbekk A, Walderhaug E, Otterholt E, Nordfjærn T. Predictors of dropout from inpatient substance use treatment: a prospective cohort study. *Subst Abuse*. 2018;12:1178221818760551. doi:10.1177/1178221818760551
17. Brorson HH, Ajo Arnevik E, Rand-Hendriksen K, Duckert F. Drop-out from addiction treatment: a systematic review of risk factors. *Clin Psychol Rev*. 2013;33(8):1010–1024. doi:10.1016/j.cpr.2013.07.007
18. Andersson HW, Otterholt E, Gråwe RW. Patient satisfaction with treatments and outcomes in residential addiction institutions. *Nord Stud Alcohol Drugs*. 2017;34(5):375–384. doi:10.1177/1455072517718456
19. Brorson HH, Arnevik EA, Rand K. Predicting dropout from inpatient substance use disorder treatment: a prospective validation study of the OQ-analyst. *Subst Abuse*. 2019;13. doi:10.1177/1178221819866181
20. Lintzeris N, Monds LA, Rivas G, Leung S, Withall A, Draper B. The Australian treatment outcomes profile instrument as a clinical tool for older alcohol and other drug clients: a validation study. *Drug Alcohol Rev*. 2016;35:6. doi:10.1111/dar.12393
21. Campbell A, Hemsley S. Outcome rating scale and session rating scale in psychological practice: clinical utility of ultra-brief measures. *Clin Psychol*. 2009;13(1):1–9. doi:10.1080/13284200802676391
22. Lambert MJ, Hansen NB, Finch AE. Patient-focused research: using patient outcome data to enhance treatment effects. *J Consult Clin Psychol*. 2001;69(2):2. doi:10.1037/0022-006X.69.2.159
23. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science*. 1977;196(4286):129–196. doi:10.1126/science.847460
24. Stallvik M. Biopsykososial tilnærming til rusavhengighet. *Rusfag*. 2011;1:105–112.
25. Marlatt GA, Baer JS, Donovan DM, Kivlahan DR. Addictive behaviors: etiology and treatment. *Ann Rev Psychol*. 1988;39:223–252. doi:10.1146/annurev.ps.39.020188.001255
26. Volpicelli J, Pettinati R, McLellan HM, et al. The biopsychosocial understanding of addiction. In: *Combining Medication and Psychosocial Treatments for Addictions: The BRENDA Approach*. New York, NY: Guilford Press; 2001:3–15.
27. Daughters SB, Richards JM, Gorka SM, Sinha R. HPA axis response to psychological stress and treatment retention in residential substance abuse treatment: a prospective study. *Drug Alcohol Depend*. 2009;105(3):202–208. doi:10.1016/j.drugalcdep.2009.06.026
28. Daughters SB, Lejuez CW, Bornovalova MA, Kahler CW, Strong DR, Brown RA. Distress tolerance as a predictor of early treatment dropout in a residential substance abuse treatment facility. *J Abnorm Psychol*. 2005;114(4):729–734. doi:10.1037/0021-843X.114.4.729
29. Rozynko VV, Stein KB. Social and psychological factors associated with length of stay in a drug treatment facility. *Int J Addict*. 1974;9(6):873–878. doi:10.3109/10826087409022181
30. Dziurkowska E, Wesolowski M. Cortisol as a biomarker of mental disorder severity. *J Clin Med*. 2021;10(21):5204. doi:10.3390/jcm10215204
31. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology*. 2009;34(2):163–171. doi:10.1016/J.PSYNEUEN.2008.10.026
32. Junghanns K, Tietz U, Dibbelt L, et al. Attenuated salivary cortisol secretion under cue exposure is associated with early relapse. *Alcohol Alcohol*. 2005;40(1):80–85. doi:10.1093/ALCALC/AGH107
33. Moss HB, Vanyukov MM, Martin CS. Salivary cortisol responses and the risk for substance abuse in prepubertal boys. *Biol Psychiatry*. 1995;38(8):547–555. doi:10.1016/0006-3223(94)00382-D
34. Szabo YZ, Breeding T, Hejl C, Guleria RS, Nelson SM, Zambrano-Vazquez L. Cortisol as a biomarker of alcohol use in combat veterans: a literature review and framework for future research. *J Dual Diagn*. 2020;16(3):322–335. doi:10.1080/15504263.2020.1771504
35. Lovallo WR, Cohoon AJ, Sorocco KH. Early-life adversity and blunted stress reactivity as predictors of alcohol and drug use in persons with COMT (rs4680) Val158Met genotypes. *Alcohol Clin Exp Res*. 2019;43(7):1519–1527. doi:10.1111/acer.14079
36. Adinoff B, Junghanns K, Kiefer F, Krishnan-Sarin S. Suppression of the HPA axis stress-response: implications for relapse. *Alcohol Clin Exp Res*. 2005;29(7):1351. doi:10.1097/01.ALC.0000176356.97620.84
37. Sinha R. New findings on biological factors predicting addiction relapse vulnerability. *Curr Psychiatry Rep*. 2011;13(5):398–405. doi:10.1007/s11920-011-0224-0
38. Jaremko KM, Sterling RC, van Bockstaele EJ. Psychological and physiological stress negatively impacts early engagement and retention of opioid-dependent individuals on methadone maintenance. *J Subst Abuse Treat*. 2015;48(1):117–127. doi:10.1016/j.jsat.2014.08.006
39. Sinha R. How does stress increase risk of drug abuse and relapse? *Psychopharmacology*. 2001;158(4):343–359. doi:10.1007/s002130100917
40. Ali B, Green KM, Daughters SB, Lejuez CW. Distress tolerance interacts with circumstances, motivation, and readiness to predict substance abuse treatment retention. *Addict Behav*. 2017;73:99–104. PMID: 28500908; PMCID: PMC5542844. doi:10.1016/j.addbeh.2017.04.016
41. Gragera-Martinez Á, León-Justel A, Arriero LH, Alor FB, Vazquez IR. Cortisol in saliva to predict relapse in patients addicted to cocaine use. *Clin Chim Acta*. 2019;493:S328–S329. doi:10.1016/j.cca.2019.03.712
42. Sinha R, Garcia M, Paliwal P, Kreek MJ, Rounsaville BJ. Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Arch Gen Psychiatry*. 2006;63(3):324–331. doi:10.1001/archpsyc.63.3.324
43. Fox HC, Jackson ED, Sinha R. Elevated cortisol and learning and memory deficits in cocaine dependent individuals: relationship to relapse outcomes. *Psychoneuroendocrinology*. 2009;34(8):1198–1207. doi:10.1016/J.PSYNEUEN.2009.03.007
44. Contoreggi C, Herning RI, Koeppl B, et al. Treatment-seeking inpatient cocaine abusers show hypothalamic dysregulation of both basal prolactin and cortisol secretion. *Neuroendocrinology*. 2003;78(3):154–162. doi:10.1159/000072797
45. Wisniewski AB, Brown TT, John M, et al. Cortisol levels and depression in men and women using heroin and cocaine. Auernhammer Brockmeyer Brown Brown Cami Cooper Facchinetti Golub Golub Greene Heim Jiang Kuhn Laudat Leserman Linkowski Lortholary Martin Mayo Nock Plotsky Rubin Varghese Villette Wisniewski Wizemann Young Zhou A, ed. *Psychoneuroendocrinology*. 2006;31(2):250–255. doi:10.1016/j.psyneuen.2005.08.002
46. Rao U, Hammen CL, Poland RE. Mechanisms underlying the comorbidity between depressive and addictive disorders in adolescents: interactions between stress and HPA activity. *Am J Psychiatry*. 2009;166(3):361–369. doi:10.1176/appi.ajp.2008.08030412

47. Adinoff B, Iranmanesh A, Veldhuis J, Fisher L. Disturbances of the stress response: the role of the HPA axis during alcohol withdrawal and abstinence. *Alcohol Health Res World*. 1998;22(1):67.
48. Adinoff B, Krebaum SR, Chandler PA, Ye W, Brown MB, Williams MJ. Dissection of hypothalamic-pituitary-adrenal axis pathology in 1-month-abstinent alcohol-dependent men, part 1: adrenocortical and pituitary glucocorticoid responsiveness. *Alcohol Clin Exp Res*. 2005;29(4):517–527. doi:10.1097/01.ALC.0000158940.05529.0A
49. Cuttler C, Spradlin A, Nusbaum AT, Whitney P, Hinson JM, McLaughlin RJ. Blunted stress reactivity in chronic cannabis users. *Psychopharmacology*. 2017;234(15):2299–2309. doi:10.1007/S00213-017-4648-Z/FIGURES/5
50. Stephens MAC, Wand G. Stress and the HPA Axis Role of Glucocorticoids in Alcohol Dependence. *Alcohol res*. 2012;34(4):468–483.
51. Peles E, Malik E, Altman Y, et al. Stress indices in methadone maintenance treatment - cross sectional and follow up study. *Psychiatry Res*. 2020;291:113218. doi:10.1016/J.PSYCHRES.2020.113218
52. Bøhle K, Otterholt E, Bjørkly S. Is there an association between salivary cortisol and dropping out of inpatient substance addiction treatments? A prospective repeated measures study. *Subst Abuse*. 2022;16. doi:10.1177/11782218221106797
53. Santucci K. Psychiatric disease and drug abuse. *Curr Opin Pediatr*. 2012;24(2):233–237. doi:10.1097/MOP.0B013E3283504FBF
54. Burdzovic Andreas J, Lauritzen G, Nordfjærn T. Co-occurrence between mental distress and poly-drug use: a ten year prospective study of patients from substance abuse treatment. *Addict Behav*. 2015;48:71–78. doi:10.1016/j.addbeh.2015.05.001
55. Løberg EM, Helle S, Nygard M, et al. The cannabis pathway to non-affective psychosis may reflect less neurobiological vulnerability. *Front Psychiatry*. 2014;5(OCT):159. doi:10.3389/fpsyt.2014.00159
56. Bramness JG, Gundersen ØH, Guterstam J, et al. Amphetamine-induced psychosis - a separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry*. 2012;12(1):1–7. doi:10.1186/1471-244X-12-221/FIGURES/1
57. Landheim AS, Bakken K, Vaglum P. Impact of comorbid psychiatric disorders on the outcome of substance abusers: a six year prospective follow-up in two Norwegian counties. *BMC Psychiatry*. 2006;6(1). doi:10.1186/1471-244X-6-44
58. Simpson DD, Joe G, Rowan-Szal GA, Greener JM. Drug abuse treatment process components that improve retention outcome assessment of correctional treatment view project TERESA view project. *J Subst Abuse Treat*. 1997;14(6):565–572. doi:10.1016/S0740-5472(97)00181-5
59. Hassel A, Nordfjaern T, Hagen R. Journal of substance use psychological and interpersonal distress among patients with substance use disorders: are these factors associated with continued drug use and do they change during treatment?) Psychological and interpersonal distress among patients with substance use disorders: are these factors associated with continued drug use and do they change during treatment? *J Subst Use*. 2012;18(5):363–376. doi:10.3109/14659891.2012.685122
60. Ormbostad HAK, Otterholt E, Stallvik M. Investigating patients' perceptions of residential substance use treatment. Is drop out a deliberate or impulsive act? *J Soc Work Pract Addict*. 2021;21(3):255–272. doi:10.1080/1533256X.2021.1933850
61. Adinoff B, Martin PR, Bone GHA, et al. Hypothalamic-pituitary-adrenal axis functioning and cerebrospinal fluid corticotropin releasing hormone and corticotropin levels in alcoholics after recent and long-term abstinence. *Arch Gen Psychiatry*. 1990;47(4):325–330. doi:10.1001/ARCHPSYC.1990.01810160025004
62. Carr WA, Ball SA. Predictors and treatment outcomes of perceived ward atmosphere among therapeutic community residents. *J Subst Abuse Treat*. 2014;46(5):567–573. doi:10.1016/j.jsat.2014.01.003
63. Verinis JS. Ward atmosphere as a factor in irregular discharge from an alcohol rehabilitation unit. *Int J Addict*. 1983;18(6):895–899. doi:10.3109/10826088309033057
64. Fischer J. The relationship between alcoholic patients' milieu perception and measures of their drinking during a brief follow-up period. *Int J Addict*. 2009;14(8):1151–1156. doi:10.3109/10826087909048704
65. Beckwith M, Best D, Dingle G, Perryman C, Lubman D. Alcoholism treatment quarterly predictors of flexibility in social identity among people entering a therapeutic community for substance abuse. *Alcohol Treat Q*. 2015;33(1):93–104. doi:10.1080/07347324.2015.982465
66. Moos RH. *Ward Atmosphere Scale Manual (A Social Climate Scale)*. Paolo Alto: Consulting Psychologists Press; 1974.
67. Moos RH, Shelton R, Petty C. Perceived ward climate and treatment outcome. *J Abnorm Psychol*. 1973;82(2):291–298. doi:10.1037/h0035184
68. McKellar J, Kelly J, Harris A, Moos R. Pretreatment and during treatment risk factors for dropout among patients with substance use disorders. *Addict Behav*. 2006;31(3):450–460. doi:10.1016/J.ADDBEH.2005.05.024
69. Marrero CA, Robles RR, Colón HM, et al. Factors associated with drug treatment dropout among injection drug users in Puerto Rico. *Addict Behav*. 2005;30(2):397–402. doi:10.1016/j.addbeh.2004.05.024
70. Taxman FS, Thanner M, Weisburd D. Risk, Need, and Responsivity (RNR): it all depends. *Crime Delinq*. 2006;52(1):28–51. doi:10.1177/0011128705281754
71. Stallvik M, Gastfriend DR, Nordahl HM. Matching patients with substance use disorder to optimal level of care with the ASAM criteria software. *J Subst Use*. 2014;20(6):389–398. doi:10.3109/14659891.2014.934305
72. Lappan SN, Brown AW, Hendricks PS. Dropout rates of in-person psychosocial substance use disorder treatments: a systematic review and meta-analysis. *Addiction*. 2020;115(2):201–217. doi:10.1111/ADD.14793
73. Miller WR. Motivation for treatment. A review with special emphasis on alcoholism. *Psychol Bull*. 1985;98(1):84–107. doi:10.1037/0033-2909.98.1.84
74. Simpson DD, Joe GW. Motivation as a predictor of early dropout from drug abuse treatment. *Psychotherapy*. 1993;30(2):357–368. doi:10.1037/0033-3204.30.2.357
75. Philips B, Wennberg P. The importance of therapy motivation for patients with substance use disorders. *Psychotherapy*. 2014;51(4):555–562. doi:10.1037/A0033360
76. Joe GW, Simpson D, Broome KM. Effects of readiness for drug abuse treatment on client retention and assessment of process. *Addiction*. 1998;93(8):1177–1190. doi:10.1080/09652149835008
77. Sacks S, McKendrick K, Sacks JY, Cleland CM. Modified therapeutic community for co-occurring disorders: single investigator meta-analysis. *Subst Abuse*. 2010;31(3):146–161. doi:10.1080/08897077.2010.495662
78. Adam EK, Kumari M. Assessing salivary cortisol in large-scale, epidemiological research. *Psychoneuroendocrinology*. 2009;34(10):1423–1436. doi:10.1016/J.PSYNEUEN.2009.06.011
79. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*. 2003;28(7):916–931. doi:10.1016/S0306-4530(02)00108-7

80. Stalder T, Kirschbaum C, Kudielka BM, et al. Assessment of the cortisol awakening response: expert consensus guidelines. *Psychoneuroendocrinology*. 2016;63:414–432. doi:10.1016/j.psyneuen.2015.10.010
81. Nicholson LM, Miller AM, Schwertz D, Sorokin O. Gender differences in acculturation, stress, and salivary cortisol response among former soviet immigrants. *J Immigr Minor Health*. 2013;15(3):540–552. doi:10.1007/S10903-012-9752-X/TABLES/3
82. Dmitrieva NO, Almeida DM, Dmitrieva J, Loken E, Pieper CF. A day-centered approach to modeling cortisol: diurnal cortisol profiles and their associations among U.S. adults. *Psychoneuroendocrinology*. 2013;38(10):2354–2365. doi:10.1016/J.PSYNEUEN.2013.05.003
83. de Leon G, Melnick G, Kressel D, Jainchill N. Circumstances, motivation, readiness, and suitability (the CMRS scales): predicting retention in therapeutic community treatment. *Am J Drug Alcohol Abuse*. 1994;20(4):495–515. doi:10.3109/00952999409109186
84. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci*. 1974;19(1):1–15. doi:10.1002/bs.3830190102
85. Strand BH, Dalgard S, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry*. 2003;57(2):113–118. doi:10.1080/08039480310000932
86. Winhusen T, Kropp F, Babcock D, et al. Motivational enhancement therapy to improve treatment utilization and outcome in pregnant substance users. *J Subst Abuse Treat*. 2008;35(2):161–173. doi:10.1016/j.jsat.2007.09.006
87. Martino S, Paris MJ, Anez L, et al. The effectiveness and cost of clinical supervision for motivational interviewing: a randomized controlled trial. *J Subst Abuse Treat*. 2016;68:11–23. doi:10.1016/j.jsat.2016.04.005
88. Santa Ana EJ, LaRowe SD, Armeson K, Lamb KE, Hartwell K. Impact of group motivational interviewing on enhancing treatment engagement for homeless veterans with nicotine dependence and other substance use disorders: a pilot investigation. *Am J Addict*. 2016;25(7):533–541. doi:10.1111/ajad.12426
89. Smedslund G, Berg RC, Hammerstrom KT, et al. Motivational interviewing for substance abuse. *Cochrane Database Syst Rev*. 2011;5:CD008063. doi:10.1002/14651858.CD008063.pub2
90. Broome KM, Joe GW, Simpson DD. Engagement models for adolescents in DATOS-A. *J Adolesc Res*. 2001;16(6):608–623.
91. Manetti L, Cavagnini F, Martino E, Ambrogio A. Effects of cocaine on the hypothalamic-pituitary-adrenal axis. *J Endocrinol Invest*. 2014;37(8):701–708. doi:10.1007/s40618-014-0091-8
92. Haney M, Ward AS, Gerra G, Foltin RW. Neuroendocrine effects of d-fenfluramine and bromocriptine following repeated smoked cocaine in humans. *Drug Alcohol Depend*. 2001;64(1):63–73. doi:10.1016/S0376-8716(00)00232-5
93. Wemm SE, Sinha R. Drug-induced stress responses and addiction risk and relapse. *Neurobiol Stress*. 2019;10:100148. doi:10.1016/J.YNSTR.2019.100148
94. Aujla H, Martin-Fardon R, Weiss F. Rats with extended access to cocaine exhibit increased stress reactivity and sensitivity to the anxiolytic-like effects of the mGluR 2/3 agonist LY379268 during abstinence. *Neuropsychopharmacology*. 2007;33(8):1818–1826. doi:10.1038/sj.npp.1301588
95. Kreek MJ, Koob GF. Drug dependence: stress and dysregulation of brain reward pathways. *Drug Alcohol Depend*. 1998;51(1–2):23–47. doi:10.1016/S0376-8716(98
96. Koob G, Kreek MJ. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *Am J Psychiatry*. 2007;164(8):1149–1159. doi:10.1176/APPI.AJP.2007.05030503/ASSET/IMAGES/LARGE/S16F7.JPEG
97. Booth BM, Curran G, Han X, et al. Longitudinal relationship between psychological distress and multiple substance use: results from a three-year multisite natural-history study of rural stimulant users. *J Stud Alcohol Drugs*. 2015;71(2):258–267. doi:10.15288/JSAD.2010.71.258
98. Ries R, Wolitzky-Taylor KB, Operskalski JT, Craske MG, Roy-Byrne P. Treatment of comorbid substance use and anxiety disorders: a case study. *J Addict Med*. 2011;5(4):248–253. doi:10.1097/ADM.0b013e318233d64b
99. Monitoring Centre for Drugs E, Addiction D. Co-morbid substance use and mental disorders in Europe: a review of the data. EMCDDA Papers. Luxembourg: Publications office of the European Union; 2013. doi:10.2810/725386.