Is There an Association Between Salivary Cortisol and Dropping Out of Inpatient Substance Addiction Treatments? A Prospective Repeated Measures Study

Substance Abuse: Research and Treatment
Volume 16: 1–11
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/11782218221106797

Kari Bøhle[1], Eli Otterholt[2] and Stål Bjørkly[3]

[1]Faculty of Health and Social Sciences, Molde University College, Clinic of Mental Health and Addiction, Møre and Romsdal Hospital Trust, Molde, Norway. [2]Clinic of Mental Health and Addiction, Møre and Romsdal Hospital Trust, Faculty of Health and Social Sciences, Molde University College, Molde, Norway. [3]Faculty of Health and Social Sciences, Molde University College, Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, Molde, Norway.

ABSTRACT: Several studies have found an association between salivary cortisol levels and dropping out of inpatient substance addiction treatment programs. The results are mixed due to variations in the study design and the lack of standardized routines for cortisol assessment. The aim of this study was to investigate whether there was (1) an association between salivary cortisol levels and dropping out from inpatient substance addiction treatments; (2) higher predictive validity for dropout in one of the cortisol indexes: Area Under the Curve with respect to ground (AUC_G) or Daily Cortisol Slope (DCS); (3) an interaction effect with time for each cortisol index; and (4) different dropout rates for sex and patients in short-term versus long-term treatment programs. This was a prospective, repeated-measures observational study. Patients (n = 173) were recruited from 2 inpatient facilities in the central region of Norway between 2018 and 2021. Salivary cortisol was measured 4 times during the treatment period, with 8 samples collected over 2 consecutive days at each time point. Cortisol levels were calculated using the cortisol indices AUC_G and DCS. Dropout was used as the outcome measure at each time point. Associations were calculated using a logistic linear regression. The results suggest a main effect of AUC_G, whereby higher levels reduce dropout risk (OR = 0.92, $P = .047$). An interaction with time in treatment also revealed a higher dropout risk (OR = 1.09, $P = .044$) during week 4 of the treatment, depending on the AUC_G. These results support using AUC_G as the recommended index when assessing cortisol, and that the relationship between cortisol levels and length of treatment should be further investigated.

KEYWORDS: Inpatient treatment, dropout, physiological stress, salivary cortisol, prospective study, biomarker, repeated measures, substance addition

RECEIVED: February 11, 2022. **ACCEPTED:** May 21, 2022.

TYPE: Original Research

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was funded by a grant from The Liaison Committee for Education (46055500-23), Research and Innovation in Central Norway.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Kari Bøhle, Faculty of Health and Social Sciences, Molde University College, Clinic of Mental Health and Addiction, Møre and Romsdal Hospital Trust, Britvegen 2, Molde, 6410, Norway. Email: kari.bohle@himolde.no

Introduction

The is a growing body of literature investigating the biological markers related to substance addiction disorders.[1,2] Evidence accumulated over the last 15 years points to the stress hormone cortisol as a possible biomarker for both vulnerability to substance addiction and relapse.[3-7] However, studies exploring the relationship between physiological stress levels and retention have yielded conflicting results.[2,8-10] As there is significant variation in study designs, sampling, and calculation procedures, more prospective studies investigating the relationship between salivary cortisol and dropout rates are necessary.[2,11,12] Thus far, a standardized routine for how and when to measure salivary cortisol levels has not been established. Instead, recent research has focused on cortisol indices.[13,14]

Treatment dropout

High dropout rates and the complexity of substance use disorders (SUDs), particularly how they are developed and maintained, are considered one of the greatest challenges in psychiatry.[8,15] The dropout rate varies between 17% and 57%, depending on how it is defined.[16,17] Furthermore, the association between the length of treatment and positive outcomes[18-20] underlines the importance of risk assessment and the prevention of treatment dropout. There is a growing body of evidence on the risk factors for dropping out.[16,21-28] Brorson et al[16] reviewed 122 studies in 2013, and found that although the studies were inconclusive, younger age was the most consistent risk factor. Ninety-one percent of the studies focused on enduring factors, such as gender and sociodemographic background. This finding emphasized the need for more research on risk factors that could be assessed during treatment.

Building upon the co-occurrence of substance addiction and mental health disorders,[29-33] several studies have found an association between psychological distress and retention in residential substance addiction treatment.[20,27,33-35] Owing to anxiety-reducing and stress-relieving properties, stress has been suggested as a motivator to consume alcohol or other substances.[36] This is compatible with the self-medication model, which asserts the use of positive or negative reinforcement to

boost positive affect.[37] Chronic consumption of alcohol and other substances may also affect the stress response system, which can lead to further cravings of substance consumption, thereby enhancing the risk of substance addiction.[12]

Growing evidence points toward the hypothalamic-pituitary-adrenal (HPA) axis in the development, maintenance, and relapse probability of substance addiction disorders.[1,12,36-45] Cortisol, which is released in response to stress, regulates the hypothalamic-pituitary-adrenal axis. In contrast, deregulation of the HPA axis is related to negative health outcomes, including cognitive decline and mental disorders,[46,47] while chronic stress is linked to both hypo- and hypercortisolism.[48] Since emotions and behavior are affected by cortisol, this may increase people's cravings and vulnerability to relapse.[49,50]

Cortisol indexes

In the early stages of salivary cortisol research, a single measure of salivary cortisol was used to assess HPA axis function.[13] Due to the fluctuating nature and circadian rhythm of cortisol, a single sampling of cortisol or average diurnal levels of cortisol are no longer considered reliable measures to investigate the function of the HPA axis.[13] The circadian rhythm of cortisol (whereby levels are higher upon wakening) peaks 30 to 45 minutes after waking up, and then declines throughout the rest of the day; this represents a basis for the recommended 3 main indexes that are often used in assessing HPA axis functioning.[47,51] The 3 indexes recommended by Ryan et al[13] are the size of the rise in cortisol post-wakening (the cortisol awakening response, CAR), the degree of change in cortisol over the waking day (diurnal cortisol slope, DCS), and the area under the curve (AUC).[13,47,51,52] Deviations in the CAR pattern have been linked to poor mental health[53] and a disruption in the HPA axis.[47] A growing body of literature suggests that DCS is particularly sensitive to psychological distress,[51,52] with a flattened DCS throughout the day.[51,54]

When several time points are considered, AUC is a frequently used index, which allows researchers to simplify the statistical analysis. Pruessner et al[14] presented 2 formulas for the computation of the AUC: *area under the curve with respect to an increase (AUC_I)* and *area under the curve with respect to the ground (AUC_G)*. They argued that the associations with other variables are dependent on the formula used.[14] While AUC_G is assumed to be more related to hormonal output, AUC_I is regarded as related to the sensitivity of the endocrine system[55] (the latter is seldom used by scientists).

Cortisol as a predictor of dropping out from substance addiction treatment

In a 2011 review, Sinha[2] focused on recent studies investigating biological factors in the prediction of dropout and relapse of substance addiction. The findings indicate that factors such as clinical, contextual, subjective, and behavioral measures can function as predictors of relapse. However, Sinha et al emphasized the need for suitable biomarkers of relapse risk. Sinha[2] also pointed out of that more than 60% of patients dropped out or relapsed within a few weeks of treatment. Due to this, the first week of treatment is considered to be the most critical period, because anxiety levels are highest during the withdrawal period.[37,56,57] This indicates that the first week of treatment is an especially vulnerable period.

Prior research has demonstrated a relationship between cortisol levels and retention in substance addiction treatments,[8,9,58] particularly in individuals with crack and cocaine addiction,[8,9,56,58-61] opioid addiction,[10] and alcoholism.[62] However, the evidence is ambiguous, and a lack of standardized methods for the measurement of cortisol is evident. Variations in study design further complicate the possibility of comparing different studies' results.

Higher basal cortisol levels have been found to positively predict post-treatment alcohol consumption in patients with alcohol dependence,[62] whereas other studies have found an attenuated cortisol response in the same population.[50,63] A blunted stress cortisol response has also been observed in individuals with cannabis addiction,[64] heroin addiction,[65] and polysubstance addiction.[66] There are also indications that there are different cortisol responses depending on the substance used, with attenuated cortisol responses found in abstinent persons with cocaine-addiction and protracted during alcohol withdrawal.[60,61,63]

For individuals recovering from substance addiction, some studies suggest that the HPA axis and cortisol levels are normalized in long-term abstainers,[67] such that cortisol responses are similar in healthy controls and patients with alcohol disorder staying abstinent.[68] This was also found in patients in methadone maintenance treatment, whereby stress levels normalized after 6 months of treatment.[69] However, few studies have investigated this development over time because most research is based on single measurements of cortisol levels.

In a prospective study conducted in 2005,[9] the HPA axis response to stress and treatment retention showed higher cortisol values in people that dropped out of treatment compared to those that completed the program. This is the first study to document cortisol as a predictor of dropout. In another prospective study on individuals with cocaine-dependence admitted to inpatient treatment, stress-induced cocaine cravings and hypothalamic-pituitary-adrenal responses were found to be predictive of cocaine relapse outcomes.[60] Greater stress-induced, but not drug cue-induced, cocaine cravings were associated with a shorter time to cocaine relapse. Stress-induced physiological responses and corticotropin and cortisol levels predicted a higher quantity of cocaine use per substance abuse episode during the follow-up period (90 days).[60] In a 2015 study, Jaremko et al[10] investigated both psychological and physiological stress in individuals with opioid-dependency. They found that abnormal cortisol levels at high and low

concentrations increased the risk of dropout by 7.7 times.[10] The study also demonstrated that patients who dropped out of treatment exhibited poor treatment engagement, elevated withdrawal symptoms, psychological distress, and abnormal cortisol levels.[10] The first prospective study evaluating basal cortisol and retention in persons with crack-cocaine-dependency was conducted in 2020,[8] and it found that increased cortisol levels were a predictor of dropping out. Their cortisol measures were based on morning levels of salivary cortisol, excluding the cortisol awakening response (CAR).

Several researchers have emphasized the importance of prospective studies when assessing the relationship between biological markers and dropout rates.[2,52] The development of stress and cortisol levels during the course of treatment may have important clinical implications and may identify areas for improving clinical services.

The present study builds on the aforementioned findings and recommendations regarding the need for prospective studies targeting biological markers for dropout in residential addiction treatment. This study aimed to investigate if there was

1. an association between salivary cortisol levels and dropping out from inpatient substance addiction treatment
2. higher predictive validity for dropouts in one of the cortisol indexes: AUC_G or DCS
3. an interaction with time for each cortisol index
4. different dropout rates depending on sex and short- vs long-term treatment

Method

Study design and setting

This observational study had a prospective naturalistic design in a cohort of patients admitted for inpatient treatment of SA. Two clinics (one short-term over a period of 2 months and one long-term over a period of 6 months) participated in the study. Both clinics are located in the middle region of Norway. The clinics provide inpatient treatment programs for people aged 18 and above with severe substance addiction problems, including polysubstance addiction; in 2020, they had 24 (short-term) and 15 (long-term) treatment beds.

A combination of individual, milieu, and group therapy is offered at both clinics. The staff had a multidisciplinary background, including psychologists, psychiatrists, social workers, occupational therapists, nurses, physical therapists, and other trained staff. The treatment facilities also offer physical activities and training. Individual adjustments are made according to each patients' needs. The main goal of the treatment is to strengthen the individual's coping and overall functioning.

The long-term institution has a somewhat different treatment structure than the short-term clinic. The treatment is based upon a modified therapeutic community approach[70] where patients are required to take an active part in their own and co-patients' treatment. Taking part in the daily life of the community is a core concept, as the milieu therapy is based on "here and now"-situations. The program is organized stepwise, with increasing responsibility and different roles in the community for each step.

Recruitment and study participants

Inclusion criteria were being admitted to voluntary treatment or treatment according to the execution of the sentence act: §12.[a] All the study participants were over 18 years old. The majority of the participants came from the catchment area of a regional health trust. The exclusion criteria were involuntary admission, detoxification stay, or patients judged mentally or physically incapable of providing consent on the day of data collection (a decision that was made by the clinical staff). Recruitment was performed during the first treatment week, either by one of the primary authors (K.B.) or by a research assistant. The patients received both oral and written information about the study before they signed the informed consent form. Participating in the study was voluntary and choosing not to participate had no consequences for the individual's treatment plan. Those who wanted time to reflect on the decision to participate could do so for a couple of days. As an incentive for participation, all patients agreeing to participate in the study received a gift card of 300 NOK after the last measuring point.

Data collection was performed with repeated measures throughout the treatment stay: 8 weeks and four time points for both clinics. The four time points were the same for both clinics, starting in the second treatment week and then every 2 weeks after that point. As such, T1, T2, T3, and T4 were set to treatment weeks 2, 4, 6, and 8, respectively. Cortisol levels and retention were measured at each time point.

Measures

Baseline data were collected using information from electronic medical records and self-reported sociodemographic data at the baseline (T1), and then salivary cortisol levels were measured at all timepoints (T1-T4). The data were collected between June 2018 and October 2021. From March to September 2020, data collection was set on hold due to the COVID-19 pandemic. Following this period, the procedures were adapted according to the COVID-19 measures put in place by the Norwegian government.

Treatment dropout. Treatment dropout was defined as premature discontinuation of treatment or failure to complete the planned inpatient program. Information about dropout status (yes/no) was retrieved from the medical records at each timepoint (T1-4).

Demographic variables. Age, sex, and whether the patient was in treatment on the Execution of Sentences Act §12, were obtained from the patient records.

Previous inpatient stay, drug use, and diagnosis. Information about previous inpatient stays and years of addiction was obtained using a sociodemographic form that was handed out at T1. Information about primary SUD and other psychiatric diagnoses was obtained from medical records using the International Classification of Diseases (ICD-10, World Health Organization[71]). SUD diagnoses (F10-19) indicated the substance used. The diagnoses in the medical record were either based on clinicians' assessment of patients during their current stay or from a recent stay at a mental health or SUD treatment center. SUD diagnoses were used as categorical variables in the analysis, and psychiatric diagnoses were made continuously (*number of psychiatric diagnoses*).

Cortisol (CORT). As salivary cortisol is used as a biological indicator of psychological stress, cortisol sampling was performed at each timepoint (T1-4). To ensure internal validity, sampling was performed 4 times a day (between 08 a.m. and 16 p.m.) for 2 consecutive days at each time point (T1-4): Sampling time (ST) 1 (mean 08.39 a.m., SD = 2 minutes), ST2 (mean 10.33 a.m., SD = 2 minutes), ST3 (mean 01.04 p.m., SD = 2 minutes), ST4 (mean 02.55 p.m., SD = 2 minutes). Samples were collected using a saliva collection device (Sarstedt Nümbrecht, Germany) that consisted of a cotton swab and a sampling vessel. Saliva was used according to the manufacturer's instructions, and the participants were advised not to eat, ingest nicotine and caffeine, or brush their teeth 60 minutes prior to sampling. The participants chewed the cylindrical synthetic swab for at least 1 minute or until it was full of saliva and then returned it to the sampling tube. The saliva samples were then stored at 4°C for a maximum of 7 days before being sent to the biobank (Biobank1, Ålesund Hospital, Møre, and Romsdal Hospital Trust). During transportation, the samples were maintained at room temperature for up to 4 hours. At the laboratory, the Salivettes containing saliva were centrifuged at 2000*g* for 10 minutes, after which the synthetic swab was removed and all the saliva was transferred to the sample cups adapted to the Cobas instrument used to analyze cortisol concentration. The samples were then stored at - 80°C for up to 12 months, while waiting for further analysis.

All samples were analyzed by the Department of Medical Biochemistry, Møre, and Romsdal Hospital Trust. To reduce analytical within-subject variation, cortisol was mainly analyzed in batches for each set of participant samples (ie, up to 32 samples). Cortisol levels were measured using an immunochemical assay on a Roche Cobas 8000 e801 automated analyzer (Roche Diagnostics, Oslo, Norway). The assay had a lower detection limit of 1.5 nmol/l, and the within-run imprecision (CV%) was 3.1% (at 5 nmol/l). The between-run imprecision is CV = 3.1% at 10 nmol/l and CV = 2.1% at 32 nmol/l.

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 2 samples.[52] The area under the curve with respect to the ground (AUC_G) was calculated according to the method described by Pruessner et al.[14] The AUC_G is the total AUC of all measurements[b] for each time point, based on the mean time of day for each sample time (ST).

Concentrations of salivary cortisol exceeding 2.5 SD (standard deviation) from the mean of each sample time (ST) were excluded from the dataset before calculating the AUC_G and DCS. This exclusion criterion was chosen on the basis of Stalder et al's[47] recommendation. The medical records of each participant were also controlled/checked to ensure that no participants were prescribed medications that could affect the HPA axis and/or glucocorticoid metabolism.

Statistical analysis

For categorical variables, descriptive statistics are presented as frequency distributions. The means and SDs are presented for continuous variables. Simple and intermediate multiple logistic regression analyses were used to test the variables in the final analysis, whereby dropping out was considered the outcome. Variables included in the final model were a combination of main interest (AUC_G and DCS) and general 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 produced an adjusted logistic regression effect for dropout relative to the change in AUC, DCS, time, sex, age, institution, and SUD diagnosis. The interaction between AUC and time was included in the final model.

The variation inflation factor (VIF) was used to test for multicollinearity between the independent variables. The VIF-scores ranged from 1.173 to 2.436, indicating no multicollinearity issues. Cook's distance was used to check for potential influential cases, and no outliers were detected when the criterion was set to 1.00. Models with only the main effects and those 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 ($P \leqslant .05$). All statistical analyses were performed using Stata/SE 16.1. Statistical significance was *set at* $P \leqslant .05$.

Results

Characteristics of the study sample

Of the 196 patients who agreed to participate in the study, 173 were included in the final analysis. Seven participants dropped out of treatment between consent was given and before T1, 4 others withdrew from the study during the data collection

Table 1. Sample characteristics and a descriptive comparison of the 2 institutions.

	WHOLE SAMPLE	INSTITUTION		DROPOUT	
	TOTAL	SHORT-TERM	LONG-TERM	YES	NO
Number of subjects, n (%)	173	138 (79.8)	35 (20.2)	43 (24.2)	130 (75.14)
Dropouts, n (%)	43 (24.2)	29 (21)	14 (46.4)		
Sex					
Male, n (%)	129	101 (73.2)	28 (80)	36 (83.7)	90 (73.2)
Female, n (%)	44	37 (26.8)	7 (20)	7 (16.3)	33 (26.8)
Age, mean (SD, range)	38.94 (11.06, 20-69)	40.37 (11.35, 20-69)	33.29 (7.67-21-54)	38.95 (11.75, 22-66)	38.91 (10.72, 20-69)
§12 N (%)	12 (6.9)	7 (5.1)	5 (14.3)	2 (4.8)	8 (6.5)
Psychiatric diagnoses, mean (SD, range)	1.06 (1.24, 0-5)	1 (1.23, 0-5)	1.32 (1.28, 0-5)	0.95 (1.29, 0-5)	1.11 (1.24, 0-5)
Years of addiction n (SD, range)	14.34 (9.8, 0-60)	14.37 (10.47, 0-60)	14.20 (7.32, 3-30)	16.15 (8.13, 3-32)	14.10 (10.49, 0-60)
SUD diagnosis n (%)					
Alcohol	77 (44,5)	68 (49.3)	9 (25.7)	20 (46.5)	54 (43.9)
Opioids	19 (11)	12 (8.7)	7 (20)	5 (11.6)	12 (9.8)
Stimulants	35 (20.2)	28 (20.3)	7 (20)	11 25.6)	25 (20.3)
Cannabinoids	23 (13.3)	17 (12.3)	6 (17.1)	5 (11.6)	18 (14.6)
Sedative hypnotics	8 (4.6)	7 (5.1)	1 (2.9)	1 (2.3)	7 (5.7)
Multiple drug use	5 (2.9)	3 (2.2)	2 (5.7)	1 (2.3)	4 (3.3)
Previous inpatient treatment, n (%)					
Never, n (%)	60 (34.7)	53 (38.4)	7 (20)	10 (23.8)	48 (38.7)
1-2 times	45 (26)	33 (23.9)	12 (34.2)	7 (16.7)	13 (10.5)
3-5 times	36 (20.8)	26 (18.8)	10 (28.6)	12 (30)	44 (35.5)
More than 5	24 (13.9)	19 (13.8)	5 (14.3)	11 (26.2)	13 (10.5)

Abbreviations: N, number of participants; Range, minimum and maximum values; SD, standard deviation.

period, and 23 patients were excluded from the data set due to extreme cortisol values (2.5 SDs above the mean for each sample time: ST).

The sample was comprised of 74.6% male (n = 129) and 25.4% (n = 44) female. The age varied from 20 to 69 years, with a mean of 38.94 (SD = 11.06). The most common SUD diagnoses were alcohol dependence (44.5%, n = 77), stimulant dependence (20.2%, n = 35), cannabinoid dependence (13.3%, n = 23), and opioid dependence (11%, n = 19).

Prevalence of dropping out

A total of 43 (24.2%) patients that participated in this study dropped out of treatment. Eight patients dropped out after T1, 12 after T2, 12 after T3, and 11 after T4. The dropout rate was highest in the long-term institution and among men. Table 1 presents a descriptive comparison of dropouts and treatment completers, as well as descriptions of each institution.

Cortisol indexes

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 computed AUC_G and DCS for each time point are displayed in Table 2, which also indicates whether or not patients dropped out.

Table 2. Overview of the development of cortisol measured by AUC_G and DCS at each timepoint.

	DROPOUT	T1		T2		T3		T4	
		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

Abbreviations: DCS, diurnal cortisol slope; SD, standard deviation; T1, time point 1 during the second treatment week, T2 is in week 4, T3 is in week 6, and T4 is in week 8.

Main results

We investigated associations with dropout, and the unadjusted analysis estimated the effect of the explanatory variables (AUC_G and DCS) on dropout rates, which were adjusted for time, age, sex, institution, number of psychiatric diagnoses, years of addiction, and SUD diagnosis. The only significant association with dropout was institution, whereby patients were 64% less likely to drop out of short-term programs. Sex differences were also close to being significant, as women had a 56% lower dropout risk. Background variables such as psychiatric diagnoses and years of addiction were not significantly associated with dropping out and were therefore excluded from further analysis. However, the other non-significant variables were included in further analysis, because they were the main explanatory variables or variables of general interest in our study.

In the final multivariate logistic regression analysis (Table 3), we analyzed the association between the explanatory variables (AUC_G and DCS) and dropout, which was adjusted for time, sex, age, institution, and SUD diagnosis. The interaction between time and AUC_G was also included in this model. The analysis showed significant main effects between AUC_G, sex, institution, and dropout. The main effect for AUC_G showed that the odds for dropout decreased by 8% for each unit increase in AUC_G. AUC_G also had a significant interaction with T2 compared to T1, demonstrating 9% lower odds for dropout for each unit's increase in AUC_G. The main effects for sex and institution had 73% lower dropout odds for women and 82% reduced odds in the short-term program.

Discussion

Main findings

In this prospective naturalistic study, we investigated the association between the explanatory variables of salivary cortisol, which was measured by AUC_G and DCS, and dropout. Forty-three of the total 173 participants dropped out of the treatment during the course of study. Findings from the multiple logistic regression analysis suggest that a higher AUC_G significantly decreases the odds of dropping out of treatment, although this depends on the time of treatment. Women and those in short-term treatment programs also had significantly lower odds of dropout.

RQ1: Is there an association between cortisol levels and dropping out of inpatient addiction treatment?

The results showed that low AUC_G values were positively associated with dropping out from treatment. No significant results were obtained for the other cortisol index DSC.

Although it is well established that drug use has the potential to affect and deregulate the activity of the HPA axis, literature focusing on an altered stress response on the risk of dropout and relapse is scarce.[12] Results from previous studies have demonstrated both higher[8] and lower[50,63] cortisol levels in patients who dropped out of treatment. Due to the ambiguity of previous studies, we did not have a directional hypothesis regarding cortisol levels in the context of predicting dropout. The descriptive statistics (Table 1) showed higher AUC_G values for those who completed treatment compared to those who dropped out. In a previous study by Adinoff et al,[63] both basal and stimulated cortisol levels were attenuated in abstinent alcoholics compared to healthy controls. The lower levels of cortisol in the group of patients with alcohol dependency could be comparable to the dropouts in our study, in that lower levels of cortisol may be a sign of HPA axis hypo-reactivity in substance-dependent subjects. Whether this hypo-reactivity is the result of or the cause of chronic substance consumption remains uncertain.

Reduced cravings after cortisol administration has been found in individuals addicted to cocaine[72] and alcohol,[73] as well as in patients who received a low dose of heroin.[74,75] Findings for opioid maintenance also points to possible effects for stress-responses, in that the administration of buprenorphine seems to normalize cortisol levels.[76] As craving is considered a predictor of relapse,[75] the administration of cortisol or opioids, such as buprenorphine or naltrexone, might have pharmacological treatment potential for preventing relapse.[74,76]

The hypo-responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis could be a result of psychological

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	0.98	0.96: 1.00	.178	0.98	0.95: 1.00	.138	0.92	0.85: 0.99	.047
DCS	0.87	0.58: 1.31	.525	1.04	0.58: 1.88	.874	1.16	0.63: 2.15	.617
Time			.964			.145			.445
T1	1.00			1.00			1.00		
T2	1.62	1.12: 2.36	.964	2.24	0.70: 7.18	.171	0.10	0.00: 2.09	.140
T3	1.84	1.08: 3.14	.978	1.37	0.37: 5.09	.636	0.53	0.01: 16.42	.720
T4	2.72	1.69: 1.02	.980	3.97	1.13: 13.96	.031	0.51	0.02: 8.82	.647
Age	0.99	0.96: 1.02	.862	1.03	0.98: 1.09	.131			
Sex									
Male	1.00			1.00			1.00		
Female	0.44	0.18: 1.07	.072	0.29	0.08: 1.05	.061	0.27	0.07: 0.99	.049
Institution									
Long-term	1.00			1.00			1.00		
Short-term	0.36	0.19: 0.69	.002	0.18	0.07: 0.48	.001	0.18	0.07: 0.49	.001
Psychiatric diagnoses	0.99	0.77: 1.28	.987	-					
Years of addiction	1.02	0.99: 1.05	.095						
SUD diagnosis			.496			.471			.612
Alcohol	1.00			1.00			1.00		
Opioids	1.46	0.55: 3.84	.439	2.18	0.57: 8.30	.250	1.78	0.44: 7.20	.415
Stimulants	1.14	0.51: 2.53	.743	2.13	0.63: 7.12	.219	1.79	0.52: 6.12	.351
Cannabinoids	0.43	0.12: 1.51	.192	0.64	0.11: 3.57	.618	0.63	0.11: 3.52	.600
Sedative hypnotics	0.42	0.05: 3.27	.410	0.92	0.10: 8.53	.947	0.83	0.08: 7.81	.873
Multiple drug use	1.95	0.40: 9.28	.401	3.72	0.54: 25.27	.179	3.57	0.51: 25.09	.199
						Interaction			
						Time#c. AUC_G			.253
						T1			
						T2	1.09	1.00: 1.19	.044
						T3	1.02	0.92: 1.14	.612
						T4	1.06	0.97: 1.15	.149

Abbreviation: CI, confidence interval.

stressors.[49] Attenuated cortisol accumulation may lead to poor coping strategies in response to stress. Patients dropping out of treatment may face more difficulty managing the challenges of SUD treatment.[10]

RQ2: Higher predictive validity for dropout in one of the cortisol indexes (AUC_G, or DCS)

We used two of the recommended indices for computing cortisol levels: AUC_G and DCS.[13] The 2 indices are based on different aspects of cortisol, in that DCS is based on the diurnal rhythm of cortisol and AUC_G is regarded as a measure of total cortisol/basal cortisol levels. The fact that statistical significance was reached for AUC_G and not DCS could be due to multiple reasons. Basal cortisol levels could be more relevant in predicting dropout, even if DCS is known to be sensitive to psychological distress.[52,77] The relationship between cortisol and psychological distress in dropping out was found in other studies,[10] although it was not monitored in the current study. The main difference between AUC_G and DCS is that AUC_G takes all the measurements into account, whereas DCS only measures the difference between 2 sample times (STs). Therefore, the DCS, which was calculated based on 2 daily cortisol samples, might not have been sufficiently sensitive in this research. The AUC_G is the total area under the curve of all measurements (STs) and thus takes both the sensitivity and intensity of cortisol into account.

RQ3: An interaction with time for different cortisol indexes

The final multiple logistic regression model showed that the cortisol index AUC_G interacted with T2 in predicting dropout. The results imply that the odds of dropping out were 9% higher at the second timepoint in the fourth treatment week, depending on the AUC_G. Previous research has demonstrated that stress and cortisol levels are normalized during periods of abstinence and treatment.[67] This is supported by our finding that time interacts with cortisol levels in predicting dropout, as well as with other studies of dropout rates and cortisol levels during early abstinence.[2,78,79] As previously mentioned, some studies have indicated that early stages of abstinence and treatment are a critical period for predicting dropout,[50,80] which could possibly be linked to this finding. Looking further into the development of cortisol at each time point is beyond the scope of this article, but it seems relevant for future studies to assess this.

RQ4: Different risk of dropouts for sex and short- term versus long-term treatment

As pointed out by Brorson et al,[16] studies on the risk factors for dropping out have revealed varying results. This is also the case for sex, as there is no clear consensus on whether there is a higher risk of dropout for men compared to women. In our sample, we found that being female reduced the odds of dropping out by 72%.

Admission to short-term treatment programs results in an 81% lower risk of dropout. We suggest that there are 3 main reasons for the lower dropout rate among short-term institutions. First, long-term institutions have a longer "time at risk" of dropping out due to the length of the treatment program. Second, since the institutions serve the same catchment area, it is natural to enter a long-term treatment program after failing to get admitted into a short-term institution. Third, patient characteristics vary slightly between the 2 institutions (concerning SUD diagnosis, previous treatment experience, and a slightly younger age at the long-term clinic). This is particularly notable in the case of age, as this is one of the most consistent risk factors for dropout.[16] As mentioned in the Methods section, there is also a somewhat different structure in the long-term institution, which builds upon a modified model of a 3-step structured therapeutic community. This could explain why dropout rates are higher in long-term institutions.

Strengths and limitations

Strengths: First, the prospective design allowed for repeated measurements, providing valuable information about the development of cortisol and the time of dropout. Second, the naturalistic setting, which measured basal cortisol levels rather than stress responses, is also an advantage. To prevent dropouts, it is important to evaluate the context of dropouts during treatment. Third, for the salivary sampling procedure, several actions were taken to minimize the effect of blunted cortisol activity or "random values." This included taking 4 salivary samples a day over 2 consecutive days, as well as using 2 recommended indexes when calculating cortisol levels. Fourth, the application of 2 cortisol indices enhanced internal validity. Moreover, we used salivary samples, as this is a non-invasive procedure.

Limitations: The choice of logistic regression for data analysis can be questioned and survival analysis with Cox regression could be an alternative. However, due to the study design and data collection, logistic regression was most appropriate. From a statistical point of view there will be little difference in the results from a logistic regression and a Cox regression. It is well known that the 2 models yield similar estimates of regression coefficients in studies with short follow-up period and low incidence of event occurrence, which was the case in this study.

We did not control for the time that participants woke up and could therefore not be certain that we avoided the cortisol awakening response (CAR). Instead, all samples were inspected for unusual values, and samples exceeding 2.5 standard deviations from the mean of each sample time (ST) were excluded from further analysis. Two additional aspects that were not controlled for in the statistical analysis were stressful events in the patients' lives and the intake of nicotine and caffeine.

As the long-term clinic offers a 6-month treatment, the original plan was to include salivary samples close to the time of discharge (ie, in week 26 of the treatment). However, since only 32 participants were receiving treatment from a long-term institution, this was not optimal for the statistical analyses. Therefore, data after week 8 of treatment were not included in the statistical analyses due to poor statistical power.

In addition to the missing measurement, including a measurement that was taken before week 2 of the treatment could also be valuable for 2 reasons. First, having the first measurement in treatment week 1 would have provided additional information about the development of cortisol during treatment. Second, we could have included patients who dropped out in the first treatment week, leading to a higher number of participants.

As a final note on limitations, we want to emphasize that our results reveal a significant association between cortisol and dropout, albeit without illustrating what this represents. The purpose of this study was solely to assess the possibility of cortisol as a biomarker of dropout.

Conclusion

Our study found a significant association between the cortisol index AUC_G and dropping out, depending on the time of treatment; however, no such association was found for the DCS index. This indicates that accumulated levels of cortisol can be a potential biomarker of dropping out. The measurement of basal cortisol levels may be used as a diagnostic marker to assess dropout propensity. Assessment of cortisol at the beginning and in the middle of treatment could inform clinicians of the need to tailor interventions toward stress regulation. Psychosocial variables, such as psychological distress, the atmosphere in the ward, and motivation, should be assessed in future studies to confirm the association between basal cortisol levels and perceived stress. Monitoring other possible reasons for dropping out of treatment using a stricter sampling protocol is also recommended in future studies.

In summary, and as expected, we did not find any cortisol—dropout breakthrough in our study. Nevertheless, some small steps can help develop this important field of clinical research.

Acknowledgements

We wish to thank all the patients who agreed to participate in this study and the institutions that allowed us to implement the study. Special thanks to the participating institutions and to Marit Bævre Bergseth (HMR) for assisting with the data collection. Petter Laake (UiO) also deserves a special mention for helping with the statistical analyses. Biobank1 at Ålesund Hospital helped with the storage of salivary samples during the data collection process. We would also like to acknowledge the Department of Medical Biochemistry, Møre, and Romsdal Hospital Trust for performing the cortisol analyses. We would like to thank Editage (www.editage.com) for English language editing.

Author Contributions

The study and original protocol were designed and written by EO with contributions from SKB. The final protocol and implementation of the study were performed by KB, who was also primarily responsible for the manuscript. The statistical analyses were performed by KB, with substantial help from Petter Laake (mentioned in acknowledgments). All the authors contributed to the revision of the manuscript and approved the final version.

Ethics

The Regional Committee for Medical Research Ethics in Central Norway approved this study in January 2018 (approval #2017/2057/REK-Midt).

ORCID iD

Kari Bøhle https://orcid.org/0000-0001-7187-4010

NOTES

a. The §12 law provides the opportunity for criminal proceedings to take place in an approved inpatient treatment facility for SUD. Application for §12 is done by the individual themselves and is hence considered as voluntary.

b. The formula for AUC_G is summarized as: $AUC_G = \Sigma i = 1n-1(m_{(i+1)} + m_i)\ t_i 2$, where t_i denotes the individual time distance between measurements, m_i denotes the individual measurement, and n represents the total number of measures.

REFERENCES

1. Volkow ND, Koob G, Baler R. Biomarkers in substance use disorders. *ACS Chem Neurosci*. 2015;6:522-525.
2. Sinha R. New findings on biological factors predicting addiction relapse vulnerability. *Curr Psychiatry Rep*. 2011;13:398-405.
3. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology*. 2009;34:163-171.
4. Junghanns K, Tietz U, Dibbelt L, et al. Attenuated salivary cortisol secretion under cue exposure is associated with early relapse. *Alcohol Alcohol*. 2005;40:80-85.
5. Moss HB, Vanyukov MM, Martin CS. Salivary cortisol responses and the risk for substance abuse in prepubertal boys. *Biol Psychiatry*. 1995;38:547-555.
6. 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;16:322-335.
7. Lovallo WR, Cohoon AJ, Sorocco KH, et al. 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;43:1519-1527.
8. 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.
9. 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;105:202-208.
10. 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;48:117-127.
11. Sinha R. How does stress increase risk of drug abuse and relapse? *Psychopharmacology*. 2001;158:343-359.
12. Wemm SE, Sinha R. Drug-induced stress responses and addiction risk and relapse. *Neurobiol Stress*. 2019;10:100148.
13. Ryan R, Booth S, Spathis A, Mollart S, Clow A. Use of salivary diurnal cortisol as an outcome measure in randomised controlled trials: a systematic review. *Ann Behav Med*. 2016;50:210-36.

14. 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;28:916-931.
15. 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.
16. 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: 1010-1024.
17. Rusbehandling - avbrudd i behandlingen - Helsedirektoratet. 2018. Accessed May 11, 2021. https://www.helsedirektoratet.no/statistikk/kvalitetsindikatorer/rusbehandling/avbrudd-i-tverrfaglig-spesialisert-rusbehandling
18. Zhang Z, Friedmann PD, Gerstein DR. Does retention matter? Treatment duration and improvement in drug use. *Addiction*. 2003;98:673-684.
19. Simpson DD, Joe GW, Brown BS. Treatment retention and follow-up outcomes in the Drug Abuse Treatment Outcome Study (DATOS). *Psychol Addict Behav*. 1997;11:294-307.
20. Simpson DD, Joe GW, Rowan-Szal GA, Greener JM. Drug abuse treatment process components that improve retention. *J Subst Abuse Treat*. 1997;14:565-572.
21. Stark MJ. Dropping out of substance abuse treatment: a clinically oriented review. *Clin Psychol Rev*. 1992;12:93-116.
22. Li X, Sun H, Purl A, Marsh DC, Anis AH. Factors associated with pretreatment and treatment dropouts among clients admitted to medical withdrawal management. *J Addict Dis*. 2007;26:77-85.
23. 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;17:374-378.
24. López-Goñi JJ, Fernández-Montalvo J, Arteaga A. Addiction treatment dropout: exploring patients' characteristics. *Am J Addict*. 2012;21:78-85.
25. Baekeland F, Lundwall L. Dropping out of treatment: a critical review. *Psychol Bull*. 1975;82:738-783.
26. Darke S, Campbell G, Popple G. Retention, early dropout and treatment completion among therapeutic community admissions. *Drug Alcohol Rev*. 2012;31:64-71.
27. Andersson HW, Steinsbekk A, Walderhaug E, Otterholt E, Nordfjærn T. Predictors of dropout from inpatient substance use treatment: a prospective cohort study. *Subst Abuse Res Treat*. 2018;12:1178221818760551.
28. Andersson HW, Otterholt E, Gråwe RW. Patient satisfaction with treatments and outcomes in residential addiction institutions. *Nord Stud Alcohol Drugs*. 2017;34:375-384.
29. Bray JW, Aden B, Eggman AA, et al. Quality of life as an outcome of opioid use disorder treatment: a systematic review. *J Subst Abuse Treat*. 2017;76:88-93.
30. Morisano D, Babor TF, Robaina KA. Co-occurrence of substance use disorders with other psychiatric disorders: implications for treatment services. *Nord Stud Alcohol Drugs*. 2014;31:5-25.
31. Henwood B, Padgett DK. Reevaluating the self-medication hypothesis among the dually diagnosed. *Am J Addict*. 2007;16:160-165.
32. Andersen SL, Teicher MH. Desperately driven and no brakes: developmental stress exposure and subsequent risk for substance abuse. *Neurosci Biobehav Rev*. 2009;33:516-524.
33. 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.
34. Marcus MT, Schmitz J, Moeller FG, et al. Stress and length of stay in therapeutic community treatment for adolescents with substance use disorders. *Addict Disord Their Treat*. 2013;12:175-182.
35. Hassel A, Nordfjærn T, Hagen R. 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*. 2013;18:363-376.
36. Becker HC, Johnson Veterans RH. Effects of alcohol dependence and withdrawal on stress responsiveness and alcohol consumption. *Alcohol Res*. 2012;34:448-458.
37. Blaine SK, Sinha R. Alcohol, stress, and glucocorticoids: from risk to dependence and relapse in alcohol use disorders. *Neuropharmacol*. 2017;122:136-147.
38. Goeders NE. Stress, motivation, and drug addiction. *Curr Dir Psychol Sci*. 2004;13:33-35.
39. Kreek MJ, Koob GF. Drug dependence: stress and dysregulation of brain reward pathways. *Drug Alcohol Depend*. 1998;51:23-47.
40. Blaine SK, Seo D, Sinha R. Peripheral and prefrontal stress system markers and risk of relapse in alcoholism. *Addict Biol*. 2017;22:468-478.
41. Schwabe L, Dickinson A, Wolf OT. Stress, habits, and drug addiction: a psychoneuroendocrinological perspective. *Exp Clin Psychopharmacol*. 2011;19:53-63.
42. Back SE, Hartwell K, DeSantis SM, et al. Reactivity to laboratory stress provocation predicts relapse to cocaine. *Drug Alcohol Depend*. 2010;106:21-27.
43. Milivojevic V, Sinha R. Central and peripheral biomarkers of stress response for addiction risk and relapse vulnerability. *Trends Mol Med*. 2018;24:173-186.
44. Volkow ND. Drug abuse and mental illness: progress in understanding comorbidity. *Am J Psychiatr*. 2001;158:1181-1183.
45. Heinz A, Beck A, Grüsser SM, Grace AA, Wrase J. Identifying the neural circuitry of alcohol craving and relapse vulnerability. *Addict Biol*. 2009;14:108-118.
46. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci*. 2009;10:434-445.
47. Stalder T, Kirschbaum C, Kudielka BM, et al. Assessment of the cortisol awakening response: expert consensus guidelines. *Psychoneuroendocrinology*. 2016;63: 414-432.
48. Brady KT, Sinha R. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. *Am J Psychiatr*. 2005;162:1483-1493.
49. Adinoff B, Martin PR, Roehrich L, Moss HB. Article in archives of general psychiatry. 1990. Accessed February 2, 2022. https://www.researchgate.net/publication/233761570
50. 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: 1351-1355.
51. Adam EK, Quinn ME, Tavernier R, McQuillan MT, Dahlke KA, Gilbert KE. Diurnal cortisol slopes and mental and physical health outcomes: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2017;83:25-41.
52. Adam EK, Kumari M. Assessing salivary cortisol in large-scale, epidemiological research. *Psychoneuroendocrinology*. 2009;34:1423-1436.
53. Vrshek-Schallhorn S, Doane LD, Mineka S, Zinbarg RE, Craske MG, Adam EK. The cortisol awakening response predicts major depression: predictive stability over a 4-year follow-up and effect of depression history. *Psychol Med*. 2013;43:483-493.
54. Doane LD, Zinbarg RE, Adam EK. Are flatter diurnal cortisol rhytms associated with major depression and anxiety disorders in late adolescence? The role of life stress and daily negative emotion. *Dev Psychopathol*. 2013;25:629-642. doi:10.1017/S0954579413000060.
55. Fekedulegn DB, Andrew ME, Burchfiel CM, et al. Area under the curve and other summary indicators of repeated waking cortisol measurements. *Psychosom Med*. 2007;69:651-659.
56. Fox HC, Jackson ED, Sinha R. Elevated cortisol and learning and memory deficits in cocaine dependent individuals: relationship to relapse outcomes. *Psychoneuroendocrinology*. 2009;34:1198-1207.
57. Sinha R, Talih M, Malison R, Cooney N, Anderson GM, Kreek MJ. Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cue-induced cocaine craving states. *Psychopharmacology*. 2003;170:62-72.
58. 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;114:729-734.
59. Gragera-Martinez 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.
60. 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;63:324-331.
61. 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;78:154-162.
62. Adinoff B, Leonard D, Price J, et al. Adrenocortical sensitivity, moderated by ongoing stress, predicts drinking intensity in alcohol-dependent men. *Psychoneuroendocrinology*. 2016;76:67-76.
63. 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;29:517-527.
64. Cuttler C, Spradlin A, Nusbaum AT, Whitney P, Hinson JM, McLaughlin RJ. Blunted stress reactivity in chronic cannabis users. *Psychopharmacology*. 2017;234: 2299-2309.
65. Gerra G, Baldaro B, Zaimovic A, et al. Neuroendocrine responses to experimentally-induced emotions among abstinent opioid-dependent subjects. *Drug Alcohol Depend*. 2003;71:25-35.
66. Lovallo WR, Dickensheets SL, Myers DA, Thomas TL, Nixon SJ. Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. *Alcohol Clin Exp Res*. 2000;24:651-658.
67. Ann Stephens M, Wand G. Stress and the HPA axis role of glucocorticoids in alcohol dependence. *Alcohol Res*. 2012;34:468-483.

68. Munro CA, Oswald LM, Weerts EM, McCaul ME, Wand GS. Hormone responses to social stress in abstinent alcohol-dependent subjects and social drinkers with no history of alcohol dependence. *Alcohol Clin Exp Res*. 2005;29: 1133-1138.
69. 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.
70. Sacks S, McKendrick K, Sacks JY, Cleland CM. Modified therapeutic community for co-occurring disorders: single investigator meta analysis. *Subst Abuse*. 2010;31:146-161.
71. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Accessed January 26, 2022. http://apps.who.int/iris/handle/10665/37958
72. Elman I, D'Ambra MN, Krause S, et al. Ultrarapid opioid detoxification: effects on cardiopulmonary physiology, stress hormones and clinical outcomes. *Drug Alcohol Depend*. 2001;61:163-172.
73. Soravia LM, Moggi F, de Quervain DJ. Effects of cortisol administration on craving during in vivo exposure in patients with alcohol use disorder. *Transl Psychiatry*. 2021;11:6-9.
74. Walter M, Gerhard U, Gerlach M, Weijers HG, Boening J, Wiesbeck GA. Cortisol concentrations, stress-coping styles after withdrawal and long-term abstinence in alcohol dependence. *Addict Biol*. 2006;11:157-162.
75. Schneekloth TD, Biernacka JM, Hall-Flavin DK, et al. Alcohol craving as a predictor of relapse. *Am J Addict*. 2012;21 Suppl 1:S20-S26.
76. Bart G. Maintenance medication for opiate addiction: the foundation of recovery. *J Addict Dis*. 2012;31:207-225.
77. Adam EK. Emotion-cortisol transactions occur over multiple time scales in development: implications for research on emotion and the development of emotional disorders. *Monogr Soc Res Child Dev*. 2012;77:17-27.
78. Rasmusson AM, Marx CE, Pineles SL, et al. Neuroactive steroids and PTSD treatment. *Neurosci Lett*. 2017;649:156-163.
79. Adinoff B, Martin PR, Bone GH, 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;47:325-330.
80. Junghanns K, Horbach R, Ehrenthal D, Blank S, Backhaus J. Cortisol awakening response in abstinent alcohol-dependent patients as a marker of HPA-axis dysfunction. *Psychoneuroendocrinology*. 2007;32:1133-1137.