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Psychological and physiological stress negatively impacts early engagement and retention of opioid-dependent individuals on methadone maintenance

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Abstract

The present study investigated whether psychological and/or physiological measures of stress would impede induction onto methadone maintenance and predict early (<6 months) discontinuation. Compared with controls, opioid-dependent subjects displayed increased distress on the perceived stress scale (PSS) and post-traumatic stress disorder checklist (PCLC); 60% exhibited abnormal cortisol. Addiction severity index (ASI), drug-use, and stress indices explained between 17–37% of the variance in engagement including attendance, opioid abstinence, and methadone stabilization. Participants who discontinued treatment displayed poor engagement, abnormal cortisol, elevated withdrawal symptoms, higher distress, and increased ongoing opioid use versus compliant individuals. Discontinuation was initially related to drug-use severity; however, by 6 months, retention depended primarily upon cortisol abnormalities, which increased an individual's discontinuation risk by 7.7-fold. These findings support admission screening with the ASI/cortisol for drop out, and stress/drug-use indices for engagement that together may enable clinically-relevant early recognition and interventions for prevention of stress-induced relapse in opioid-dependent populations.

Keywords

Opioid dependence; Stress; Methadone Maintenance Treatment; Relapse Risk

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1. Introduction

Co-morbid psychiatric pathologies complicate opioid dependence treatment (Brady & Sinha, 2005; Brooner, King, Kidorf, Schmidt, & Bigelow, 1997; Kessler, Chiu, Demler, Merikangas, & Walters, 2005), and overall pre-admission psychiatric severity has been shown to predict poorer treatment outcomes (Cousins et al., 2011; A. T. McLellan, Luborsky, Woody, O'Brien, & Druley, 1983). International reports demonstrate that the prevalence of affective disorders within substance abusers is between 30–60% (Merikangas et al., 1998). Higher anxiety sensitivity and depressive symptoms have been observed in individuals who dropped out of heroin/cocaine treatment (Lejuez et al., 2008) but these psychological distress measures did not hold up in treatment-resistant populations (McHugh et al., 2013). Depression (Himelhoch et al., 2012; Park et al., 2009; Villagomez, Meyer, Lin, & Brown, 1995) and avoidant-maladaptive coping techniques (Belding, Iguchi, Lamb, Lakin, & Terry, 1996; Hyman et al., 2009) are associated with higher stress levels, and commonly co-exist in opioid-dependent individuals. Within the broad spectrum of co-morbid stress-related pathologies, an elevated prevalence of post-traumatic stress disorder (PTSD) (Brady & Sinha, 2005; Mills, Lynskey, Teesson, Ross, & Darke, 2005; Mills, Teesson, Ross, & Peters, 2006) and higher self-reported sub-syndromal stress, via the Perceived Stress Scale (PSS) (Hyman et al., 2009), have been observed in opioid abusers compared with controls.

Dichotomous differentiation via a PTSD diagnosis within methadone maintenance treatment (MMT) patients has been found to exert minimal effects on overall treatment retention (Hien, Nunes, Levin, & Fraser, 2000; Himelhoch et al., 2012; Mills et al., 2005; Mills, Teesson, Ross, & Darke, 2007b) or relapse rates (Brown, Stout, & Mueller, 1996; Norman, Tate, Anderson, & Brown, 2007), despite the presence of continued illicit drug use and poorer mental, physical and occupational functioning at follow-up compared to their non-PTSD cohorts (Clark, Masson, Delucchi, Hall, & Sees, 2001; Mills et al., 2005; Ouimette, Brown, & Najavits, 1998; Ouimette, Coolhart, Funderburk, Wade, & Brown, 2007; Read, Brown, & Kahler, 2004). A PTSD diagnosis, however, predicted a 1.5–2 fold increase in relapse rates when specifically exposed to negative interpersonal incidents and physiological cues (Norman et al., 2007). Negative emotions were likewise observed to cause more dangerous levels of intoxication and relapse in a population of PTSD diagnosed substance abusers than drug-related cues (Ouimette et al., 2007). Maladaptive coping patterns in this population also are associated with continued drug use throughout treatment (Belding et al., 1996) and greater drug use severity (Wong et al., 2013). These findings suggest that a diminished ability to manage new stress during addiction treatment may exist within a subset of incoming MMT patients and contribute to increased relapse in that population. Maladaptive processing of stressors may not be limited to patients with a PTSD diagnosis but also include those with high PTSD symptom profiles or consistently high levels of perceived stress. This could negatively impact the recovery process and has not been previously studied in the setting of induction onto an opioid agonist replacement, such as methadone.

Methadone is a long-acting opioid, which binds to the mu-opioid receptor as a full agonist and achieves steady-state circulating serum levels for continuous management (National

Institute on Drug Abuse., 2012; Ferrari, Coccia, Bertolini, & Sternieri, 2004). A stable blocking dose, which varies among patients, is achieved when opioid abstinence withdrawal symptoms are quelled, narcotic cravings are reduced, the high of other illicit opioids at their receptor are blocked, and the inherent sedation of methadone itself dissipates due to tolerance (Dole & Nyswander, 1965; Joseph, Stancliff, & Langrod, 2000; Leavitt, 2003; Nicholls, Bragaw, & Ruetsch, 2010; Nichols, Salwen, & Torrens, 1971). MMT requires daily dispensation at a federally regulated clinic, thus providing an efficacious option for individuals in need of structured comprehensive treatment (Dole & Nyswander, 1965; Gottheil, Sterling, & Weinstein, 1993; Weinstein, Gottheil, Sterling, & DeMaria, 1993). Further evidence for the negative influence of stressful stimuli have been shown, within animal studies, to trigger heroin reinstatement (Shaham et al., 1997) and although methadone was efficacious in blocking heroin/cocaine-induced reinstatement, it was unable to prevent stress-induced relapse (Leri, Tremblay, Sorge, & Stewart, 2004). The compulsory in-depth, consistent monitoring of MMT in this high-risk, less compliant patient population provided an optimal environment to examine the role of stress-related engagement and retention in opioid dependence treatment.

Functionally, stress-related co-morbidities negatively impact opioid dependence recovery by increasing cravings (Constantinou et al., 2010; Fox, Hong, Siedlarz, & Sinha, 2008; Hyman, Fox, Hong, Doebrick, & Sinha, 2007; Saladin et al., 2003) and poly-drug use (Brooner et al., 1997; K. W. Chen et al., 2011; Clark et al., 2001). Evidence of the dynamic relationship between stress and opioids has been observed at the physiological level with dysregulation of the hypothalamic-pituitary-adrenal stress axis (HPAA) in opioid addiction (Cami, Gilibert, San, & de la Torre, 1992; Daughters, Richards, Gorka, & Sinha, 2009; Willenbring et al., 1989). Cortisol (CORT) is the circulating glucocorticoid hormone that is released from the adrenal cortices and serves as the biological messenger of stress to target organs throughout the body (Hellhammer, Wust, & Kudielka, 2009; Kirschbaum & Hellhammer, 2000). Salivary CORT parallels the acute dynamic changes seen in serum cortisol and has been routinely exploited in research as a biomarker for stress and HPAA adaptation (Gozansky, Lynn, Laudenslager, & Kohrt, 2005; Tunn, Möllmann, Barth, Derendorf, & Krieg, 1992). This collection method eliminates invasive and anxiety-provoking blood collection, removes confounds of renal dysfunction in urinary samples (Hellhammer et al., 2009) and has been validated by its association with higher acute and chronic stress perception (Hirvikoski, Lindholm, Nordenstrom, Nordstrom, & Lajic, 2009; Pruessner, Hellhammer, Pruessner, & Lupien, 2003). Previous work has established HPAA disturbances exist in MMT patients (Schluger, Bart, Green, Ho, & Kreek, 2003; Schluger, Borg, Ho, & Kreek, 2001) with potentially exaggerated (Willenbring et al., 1989) or blunted (Gerra et al., 2003; Walter et al., 2011) responsiveness to stressors, on a background of hyperactivity during acute opioid withdrawal (Bearn, Buntwal, Papadopoulos, & Checkley, 2001) and hypoactivity following chronic opioid exposure (Cami et al., 1992; Facchinetti et al., 1985; Zhang et al., 2008).

Elevated CORT has been observed in individuals undergoing opioid withdrawal (Cami et al., 1992; Bearn et al., 2001). During the MMT induction process, withdrawal can occur intermittently due to the required interplay of opioid abstinence symptoms at admission, the slow federally regulated dose titration, and inter-individual differences in methadone

metabolism (Coller, Barratt, Dahlen, Loennechen, & Somogyi, 2006; Eap, Buclin, & Baumann, 2002). Throughout this transitional period, the likelihood of withdrawal symptoms escalates as the time elapsed since the previous dose of methadone increases, which exacerbates stress-related cravings (Dyer & White, 1997; Ilgen, Jain, Kim, & Trafton, 2008) and renders individuals vulnerable to psychological distress and negative moods (Elkader, Brands, Callaghan, & Sproule, 2009). Requisite time commitments from the recovery program and lifestyle changes, in the midst of continued environmental and personal drug-related cues (Epstein et al., 2014), contribute to transitional difficulties. Taken together, the initial months of induction onto methadone can be considered a stressor that coalesces with existing financial, social, medical, and legal problems to intensify the stress burden on individuals entering treatment. Unsurprisingly, an observed increase in vulnerability to relapse and drug overdose occurs during the first few weeks of treatment (Cousins et al., 2011), but comprehensive knowledge of the impact of stress regulation and perception on early MMT drop-out is lacking. To address this gap in knowledge and probe a wider range of psychological stress-related factors simultaneously, the PTSD civilian symptom checklist (PCLC) was employed, in addition to the PSS, Addiction Severity Index (ASI), and salivary CORT.

The importance of retention is illustrated by substantially decreased long-term morbidity and mortality within compliant MMT participants (Ball & Ross, 1991; Caplehorn, Dalton, Haldar, Petrenas, & Nisbet, 1996; Clausen, Anchersen, & Waal, 2008; Dole & Nyswander, 1965; Gibson & Degenhardt, 2007; Gottheil et al., 1993; Gronbladh & Ohlund, 2010; Weinstein et al., 1993). Discharge studies have indicated that more frequent or severe drug use and less education were associated with premature discontinuation (Substance Abuse and Mental Health Services Administration, 2008; Cox, Allard, Maurais, Haley, & Small, 2013). Prior work also has shown that physiological stress, such as higher cortisol responses to drug cues or stress tasks, is present in individuals who discontinue treatment prematurely (Daughters et al., 2009; Fatseas et al., 2011). The present study builds upon these findings by investigating an unprovoked perception of stress during MMT initiation, instead of in a laboratory test setting, paired with CORT as a biomarker of innate HPA axis functionality. A breakdown of early engagement measures enhances our understanding of conceivable interventions and warning signs to prevent stress-related relapse. Higher initial perceived stress levels and abnormal systemic CORT may predispose poor coping mechanisms in response to the combination of stress from external sources and initiating MMT, thereby affecting an individual's ability to manage early treatment difficulties, stabilize on a blocking dose of methadone, and ultimately establish a meaningful period of sobriety.

Our primary hypothesis posits that maladaptive and abnormal physiological responses to, and perception of, stress will be exacerbated during the tense transitional period onto methadone and predict early relapse-risk. To investigate this question, three secondary hypotheses were generated: 1) Compared with controls and normative literature values, individuals in MMT will exhibit higher indices of psychological (PSS, PCLC) and physiological stress (abnormal CORT); 2) MMT non-completers will display warning signs of higher self-reported and observed stress coping abnormalities, increased withdrawal, and poorer engagement than participants that maintained treatment during the first 6 months of the program; 3) A combination of assessments incorporating perceived stress, basal

regulation of stress, and drug severity at MMT admission will be predicative of treatment engagement and premature discontinuation. A clinically applicable and concise compilation of assessments for routine admission screening may improve personalized interventions, inform addiction treatment staff of stress-related obstacles to recovery, and reveal the susceptibility of an individual to drop out. Overall this study attempted to combine authenticated tools and expand their application to the methadone induction process for the potential prevention of stress-induced relapse.

2. Methods

2.1 Participants

Study participants included 58 opioid-dependent treatment-seeking individuals admitted to the Thomas Jefferson University Narcotic Addict Rehabilitation Program (NARP) for methadone maintenance treatment (MMT) and 28 non-opioid-dependent control individuals for baseline stress comparisons. The NARP facility is located in an economically disadvantaged section of a large northeastern U.S. city. To be eligible for admission, individuals must have met DSM-IV criteria for current opioid dependence, including documented use of greater than 1 year. Following *Internal Review Board (IRB)* approval, over an 18-month time period (January 2012 – July 2013), eligible adults (>18 years old) in MMT were recruited for study enrollment following pre-admission screening. Study exclusion criteria included court-referred treatment or participation in another MMT program within the past 30 days. Of 107 eligible individuals, 17 refused participation, 27 did not attend their scheduled study consent interview(s), and 5 failed to complete essential study materials, leaving 58 individuals as study participants. Of the 58 enrolled, 50 individuals gave usable saliva samples for cortisol (CORT) and were included in the final regression analyses. Recruitment of control subjects was done through advertisements to staff, students, and faculty within NARP and the Thomas Jefferson University campus. The control population was matched as closely as possible to the gender, racial, and age range and prevalence within the MMT study population. Control subject enrollment was voluntary; however MMT clients who completed study materials received a grocery store gift card.

2.2 Procedure & Outcome Measures

In order to substantiate the presence of elevated distress and CORT abnormalities within incoming MMT clients, following informed consent, all participants were administered the perceived stress scale (PSS) and the post-traumatic stress disorder checklist (PCLC) to assess perceived and trauma-induced psychological stress sensitivity. Saliva also was collected during the methadone admission and initiation process, for cortisol (CORT) analysis as an indicator of recent physiological stress. Control subjects underwent the same PSS, PCLC, CORT testing at a single study interview to serve as an internal control of procedural and experimental technique, as well as a comparison group for the opioid-dependent study population. A priori sample size calculations, for a minimum expected increase in of 25% on the PSS and PCLC within opioid-dependent individuals compared to controls or reference values, suggested approximately 40 participants from MMT would need to be recruited.

To more thoroughly examine the differences between participants who maintained or discontinued MMT during the initial 6 months of the program, information regarding background and persistent drug-use during treatment was collected. A detailed drug-use history was abstracted from the clinical record and included the intake Addiction Severity Index (ASI), self-reported amount of heroin used (number of bags/day), as well as benzodiazepine or marijuana use (present/absent) prior to admission. The first opioid substance an individual reported to misuse was documented based on age of initiation (heroin/pills, mainly oxycodone). Ongoing assessments were completed at clinical discretion in individual therapy sessions within a subset of MMT study participants (n=37–42), including the PSS-10, Clinical Opioid Withdrawal Scales (COWS), and self-reported days of opioid use per week. Engagement measures in treatment included medication compliance, opioid abstinence in urine drug screens (UDS), stabilization score, and group therapy attendance, which were also contrasted between MMT completers and non-completers at six months.

Engagement measures were categorical in the case of medication compliance (< or to 95% attendance at daily dosing), level of total proportional opioid-free UDS, and stabilization score, while percentage of group therapy attendance (required 4/week for 9 hours) was continuous. The frequency of UDS collection is a function of clinical judgment and often surpasses the mandated once a month minimum. The embedded bias within this clinical practice may facilitate the perception of opioid abstinence to appear disproportionately lower in individuals who were screened for opioid use more often. Therefore, the abstinence portion of the stabilization score was calculated solely using the first UDS collected in each participant every month during treatment. The concept of stabilization in MMT and possible attainment of an efficacious blocking dose of methadone was further operationalized in the stabilization score to include a participant's ability to achieve a constant methadone dose (yes/no) for at least the four weeks surrounding their 90 or 185-day post-admission date. Possible stabilization scores incorporated ongoing opioid abstinence with steady methadone dose levels, and ranged from 0–2, as follows: 0 = neither condition was met and thus no evidence of stabilization was observed, 1 = partial stabilization with a participant attaining either continuous monthly opioid-free UDS or a stable methadone dose, or 2 = both criteria are fulfilled and a participant is classified as fully stabilized at that time (Fig. 1A). All engagement measures and treatment discontinuation data was collected at 3- and 6-month intervals and censored at 90 or 185 days from MMT admission date, respectively. Stress and drug-use related predictors were incorporated into regression analyses to determine optimal screening assessments for engagement and early discontinuation risk in MMT. Treatment discontinuation was evaluated both categorically (yes/no) and continuously (days until discontinuation). Due to a dearth of literature on the expected proportion of abnormal cortisol or drop-outs during this specific time period in a comparable population, a priori sample size analysis was not done, however post-hoc power analysis supported our findings and informed where limitations in data application may exist.

2.3 Psychological Assessments

Psychological determinants of stress sensitivity were measured via the 14- and 10-item perceived stress scale (PSS) developed by Cohen (Cohen, Kamarck, & Mermelstein, 1983).

The PSS taps into the unpredictable, uncontrollable, and overloaded components of stress perception influenced by daily frustrations, major traumas, and alterations in coping abilities (Cohen & Williamson, 1988). Exploratory factor analysis on PSS items revealed a 2-factor structure: perceived distress/helplessness and perceived coping/self-efficacy (Cohen & Williamson, 1988; Hewitt, 1992; Martin, Kazarian, & Breiter, 1995; Mitchell, Crane, & Kim, 2008; Roberti, Harrington, & Storch, 2006). Notably, this assessment does not measure the amount of a pre-determined set of stressors over a given time period but one's perception of any and all individually defined stressful experiences, thus making it a superior tool for our research question. Internal consistency (Cronbach's $\alpha=0.846$ in study population) and test-retest reliability, as well as construct validation with psychiatric symptoms, overall mental health, depression, social anxiety, tolerant-inactive coping, and number of traumatic life events, have been demonstrated (Cohen et al., 1983; Lee et al., 2011; Mitchell et al., 2008; Park et al., 2009; Roberti et al., 2006; Schulze, Laudenslager, & Coussons-Read, 2009).

The PCLC was developed by Weathers as a concise assessment of the PTSD criteria outlined in the DSM-IV (Weathers, 1993) and was selected for its ability to both ascertain a total symptom intensity score, as well as having a recognized cut-off predictive of a PTSD diagnosis. The assessment consists of 17 questions about the degree of distress for each item an individual has experienced within the past month and is centered on three symptom clusters: reliving, avoidance, and hyper-arousal (Cronbach's $\alpha=0.947$ in study population). The psychometric properties of the civilian PCL (PCLC) are well established with an evidence-based recommended cut-off value of 44 for diagnostic purposes (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996; Ruggiero, Del Ben, Scotti, & Rabalais, 2003; Weathers, 1993). The ASI, version 5 (A. T. McLellan et al., 1992), was used to measure severity in seven areas that contribute to addiction, including medical, employment, legal, alcohol, drug, social/family, and psychological problems. The ASI is a frequently used, well-validated tool that is familiar to addiction staff and is regularly used for the assessment of substance abuse (A. T. McLellan et al., 1983; Meulenbeek, 2000).

2.4 Cortisol Analysis

Saliva samples from study participants were collected using the Salivette® Cortisol-specific collection system (Sarstedt Inc., Newton, NC, USA). Collection was done between 10:30AM–5:30PM $\pm$ 15 minutes following daily methadone dosing to ensure both the absence of medication anxiety and wakefulness exceeding at least one hour prior to sampling to avoid the cortisol awakening response. Individuals were instructed to place the biocompatible synthetic swab in their mouth for 45–60s. Samples were then frozen to precipitate mucins. Centrifugation of Salivettes at 1,000g was done for two minutes to isolate on average 1.1 ± 0.3 ml of clear saliva. CORT concentration was assessed by a high-sensitivity enzyme-linked immunosorbant assay (ELISA, kit ID#1-3002, Salimetrics LLC, State College, PA, USA), which has been used to calculate the correlation with serum CORT ($r(47)=0.91$, $p<0.0001$) (D'Anna-Hernandez, Ross, Natvig, & Laudenslager, 2011; Laudenslager et al., 2009). Participants' samples were run in duplicate and compared against a standard curve of known concentrations provided by Salimetrics. Each kit was validated by internal high and low CORT control samples from Salimetrics, whose concentrations

were reliably found within the 95% confidence interval provided. All preparations were read at 450nm with a standard plate reader. The optical density (OD) was averaged for duplicates, zeroed by subtraction of the OD from non-specific binding wells, normalized to blank wells, and plotted on the 4-parameter logistic curve fit for the standards. Intra- and inter-assay coefficients of variance were 5.6% and 2.5%, respectively.

To account for the effects of a potentially dysregulated physiological stress system, all abnormal CORT values were identified and collapsed, whether above or below control/normal values, into one category that signified an altered HPAA response. Values that fell above or below one standard deviation of controls (2.39–6.39 nmol/L) were recoded as “abnormal” (1, n= 10 below and 20 above) and those that fell within that range as “normal” (0, n=20). This range of CORT from internal control subjects paralleled normative values in the literature (Ahn, Lee, Choi, Kwon, & Chun, 2007; Kirschbaum & Hellhammer, 2000).

2.5 Statistics and Data Analysis

All statistical analysis was done with IBM SPSS Statistics for Windows (IBM Corp. Released 2010. Version 19.0. Armonk, NY, USA), calculated with $\alpha=0.05$, and reported as mean $\pm$ standard deviation, unless otherwise noted. Transformation of the variable “total proportional opioid-free UDS” was done because values exhibited broad variance and a significant positive skew. Three divisions were created, in lieu of log or square root transformation, to preserve interpretation of data in a meaningful way and to stratify an individual’s overall opioid abstinence from 0–25% (level 1), >25–75% (level 2), or clean urines >75% of the time (level 3).

For all regression analyses potential predictors were incorporated into the equation based on forward selection, wherein the independent variable that has the largest correlation with the dependent variable is first tested for inclusion into the model, followed by the next highest predictor, until none fit the criterion within that block/group of provided variables. This is a more stringent selection method than backward or stepwise inclusion and was chosen to avoid over-fitting estimates. Criteria for model inclusion was a significant F ($p < 0.05$) for entry and $p > 0.1$ for removal. For linear (group therapy attendance, days until discontinuation of MMT) and binary or Cox logistic regression (discontinuation status at 90 and 185 days), predictors were categorized and entered into one of the following four blocks, each screened by forward (likelihood ratio) selection; demographics (age, gender, race), drug-use indices (amount of heroin used, initiation on heroin or pills, duration of opioid use, ASI drug composite score, past benzodiazepine or marijuana use, and presence of intravenous drug use), psychological stress measures (PSS-14, PCLC score, PCLC>44 suggestive of a PTSD or not, ASI psychological composite score), or CORT-related data (abnormal CORT or not, PSSxCORT interaction term). Multinomial logistic regression (level of opioid-free urines, stabilization score) utilized the same independent variables’ main effects through the forward entry stepwise method. Additionally due to concern over under-powered analysis with several predictors, post-hoc power analysis for multiple regression was done and given the inclusion of two or less predictors in all final models with a sample size over 50, and power for all analyses was between 0.77 to 0.98. Multi-collinearity statistics were calculated for all included predictors to confirm that none

exceeded a variable inflation factor (VIF) >5 and goodness of fit tests for all logistic regressions validated rejection of the null hypotheses.

Kaplan-Meier survival analyses were done to analyze the singular contribution of stabilization score or abnormal CORT classification on premature MMT discontinuation over each time period. Cox proportional hazards regression was used to examine the impact of all collected independent intake variables (both continuously as covariates and categorically as factors) on event-based outcomes (treatment discontinuation) over a specified period of time (90 or 185 days). The assumption of proportional hazards was tested and held for abnormal CORT, first by graphical representation in log (–log) versus time with resultant parallel lines observed for CORT status. Partial residuals (Shoenfeld Residuals) also were plotted against survival time, and no significant slope/correlation different than zero ($p=0.395$) existed, despite the small number of non-censored cases.

3. Results

3.1 Evidence of increased perception of stress and psychological distress in MMT

There were no significant differences in demographics between controls, MMT participants, and MMT clients who declined or missed enrollment in the study (Table 1), suggesting generalizability within an MMT population. Baseline self-reported perceived stress (PSS-14) scores in MMT study participants were significantly higher than those reported in the general population (Cohen & Williamson, 1988) and observed within non-opioid-dependent controls (Table 1). Ongoing assessment of perceived stress levels, within a subset of MMT patients ($n=37$), also were elevated but tended to decrease throughout the study without reaching statistical significance in repeated measures analyses (data not shown). The post-traumatic stress disorder (PTSD) civilian checklist (PCLC) demonstrated that MMT participants had higher total PTSD symptom scores than controls and the majority (58.6%) scored above the diagnostic cutoff for likely PTSD, score >44 , (Blanchard et al., 1996; McDermott, Tull, Gratz, Daughters, & Lejuez, 2009; Peterlin, Ward, Lidicker, & Levin, 2007; Ruggiero et al., 2003; Saxon et al., 2001). Substantial correlations between the PSS-14 and PCLC were present in both controls ($r=0.431$, $p=0.040$) and MMT clients ($r=0.456$, $p<0.001$), in addition to a correlation with the Addiction Severity Index (ASI) psychological component in the latter ($r=0.477$, $p<0.001$).

3.2 Cortisol as a physiological marker of altered stress regulation in MMT

Although cortisol (CORT) has a canonical diurnal cycle, midday represents the least dynamic portion of the curve (Kirschbaum & Hellhammer, 2000). There was no significant difference between the average time of collection in control versus MMT participants ($t(76)=1.98$, $p>0.05$) or between sample collection time and CORT level in either group demonstrated by regression analysis. CORT was not affected by age, gender, or race in either opioid-dependent or control subjects as assessed by backward stepwise linear regression. Neither estrogen-based contraceptive use nor pregnancy was present within study participants to influence female CORT levels. The number of days enrolled in MMT, methadone dose, nor presence of opioids, marijuana, or benzodiazepines in UDS before or after saliva collection, was related to CORT values.

Salivary CORT analysis demonstrated possible physiological alterations in the HPA axis among opioid-dependent individuals. A significantly higher average CORT value was found in MMT participants compared with controls, despite a post-hoc power analysis of 70.8% (Table 1). Following categorical separation of CORT values outside one standard deviation of controls/norms, abnormally high or low CORT was present in 60.0% of MMT participants and post-hoc power analysis exceeded 86%, therefore this measure was employed for all further CORT-related analyses. Drug severity indices, such as years of opioid abuse, intravenous drug use, opioid of initiation, or amount of heroin used, did not relate to abnormal CORT. When compared with all other demographic and psychological measures, only PSS-14 score correlated with CORT category ($r=0.408$, $p=0.003$). The relationship between these variables and considerable correlations between them and engagement measures (both: $r = -0.3$, $p < 0.05$ for group therapy attendance; abnormal CORT: $r=-0.38$ and $r=-0.48$, $p < 0.01$ for opioid-free UDS percentage at each time point) warranted creation of an interaction term. The resulting predictor, PSSxCORT, can be interpreted as the contribution of perceived stress in MMT participants with CORT values outside of the normal range.

3.3 Differences in stress and engagement measures based on retention status in MMT

Of the 58 initial MMT study participants, six discontinued treatment by 90 days and fourteen prematurely left the program by 185 days (24.1%), largely due to drop-out (78.6%, plus one each: died, jailed, discharged due to violence). MMT non-completers had higher perceived stress at intake (PSS-14, Table 2) but did not significantly differ in PTSD symptoms, diagnostic level, ASI composite scores, or any drug use severity indices (data not shown). There was a significant preponderance of individuals with abnormal CORT observed within non-completers and poor engagement preceded discontinuation (Table 2). Interestingly, the association between abnormal CORT and higher perceived stress was ablated in non-completers ($r=0.229$, $p=0.497$). Individuals who prematurely left MMT also had significantly greater withdrawal symptoms during treatment, which correlated with their initial stress (PSS-14, $r=0.491$, $p=0.001$) and trended with abnormal cortisol levels. Ongoing higher stress, and continued opioid consumption was also evident in treatment drop-outs by 6 months post-admission. Significant differences between participants that dropped out before 90 days or between 91–185 days were not found by additional comparisons (data not shown).

3.4 Predictions of Treatment Engagement and Discontinuation

At 3 months post-admission 57% of participants achieved >95% daily medication compliance and the mean attendance at group therapy was 63%, which was positively impacted by a PCLC score >44 ($B = 16.89$, $p = 0.019$) and negatively affected by higher perceived stress ($B = -1.32$, $p = 0.003$; linear regression model: $\text{adj}R^2 = 0.170$, $p = 0.006$). With an average of 11.0 ± 3.6 urine drug screens (UDS) over 90 days, the majority of participants (51.7%) had fewer than 25% that were opioid-free. Abnormal cortisol increased the likelihood of classification in the lowest opioid abstinence level by 6.33 fold (likelihood ratio test (LRT): 0.029; Level 1: $p = 0.018$, Level 2: $p = 0.520$) while PCLC>44, or likely PTSD, predicted between 25–75% of UDS to be clean (LRT: 0.048; Level 1: $p = 0.222$, Level 2: $p = 0.022$; multinomial logistic regression model: $\text{pseudo}R^2 = 0.269$, $p = 0.010$).

The detrimental influence of abnormal CORT was amplified by 6 months (between the highest and lowest tiers of percent opioid-free urines (LRT: 0.003, Level 1: $\text{Exp(B)} = 19.20$, $p = 0.003$ Level 2: $\text{Exp(B)} = 7.61$, $p = 0.024$) and the amount of prior heroin use increased the RR of achieving <25% UDS opioid abstinence by 23.7% for every additional bag of heroin reported to be used per day (LRT: 0.035, Level 1: $p = 0.053$, Level 2: $p = 0.030$; multinomial logistic regression model: $\text{pseudoR}^2 = 0.373$, $p = 0.001$). Only 17.2% fulfilled both stabilization criteria in the first three months (Fig. 1B) with characteristics of heroin use and perceived stress influencing scores at both time points (3 months (model: $\text{pseudoR}^2 = 0.312$, $p = 0.003$): PSSxCORT (LRT: 0.031, 0: $\text{Exp(B)} = 1.02$, $p = 0.575$, 1: $\text{Exp(B)} = 0.97$, $p = 0.198$) and amount of heroin used (LRT: 0.010, 0: $\text{Exp(B)} = 1.37$, $p = 0.014$, 1: $\text{Exp(B)} = 1.44$, $p = 0.017$); or 6 months (model: $\text{pseudoR}^2 = 0.243$, $p = 0.016$): PSS-14 (LRT: 0.050, 0: $\text{Exp(B)} = 1.057$, $p = 0.225$, 1: $\text{Exp(B)} = 1.131$, $p = 0.022$) and the initiation on heroin vs. pills (LRT: 0.034, 0: $\text{Exp(B)} = 5.681$, $p = 0.021$, 1: $\text{Exp(B)} = 4.724$, $p = 0.056$). Overall engagement measures at six months showed a decrease in medication compliance (48% >95% compliance), consistent group therapy attendance (62–66%), roughly a third of participants classified within each stratified level of opioid abstinent urines, and 40.4% of remaining participants fully stabilized (Fig. 1B). Across these regression analyses a combination of stress and drug-related intake predictors explained between 17–37% of the variance in each engagement measure. Medication compliance failed to be predicted by any intake variables.

Categorical premature termination and the continuous number of days maintained in MMT, both demonstrated that only the ASI drug component contributed significantly to discontinuation by 3 months. Stabilization scores also were associated with MMT discontinuation and significantly predicted survival (Table 3, Fig. 2A–B). Additionally 4 of the 6 non-completers gave saliva samples, and all had abnormal CORT. Despite lack of significance by 90 days, at 6 months abnormal CORT was independently predictive of discontinuation (Table 3, Fig. 2C). Regression analysis of MMT termination by 6 months confirmed that abnormal CORT was a significant contributor but correct classification predictions were increased from 78–84% by addition of psychological indices of distress (ASI psychological, PCLC, PSS14). Number of days retained in MMT over the initial 6 months was marginally predicted by perceived stress in participants with abnormal CORT (Table 3).

To incorporate multiple potential predictors over the 185-day follow-up period, Cox regression analysis was used with forward variable selection of intake assessments (Table 3). At 3 months, only the ASI drug component was predictive with higher drug use severity dramatically increasing risk of drop-out (Table 3). At 6 months, solely abnormal CORT predicted premature MMT discontinuation, which increased risk to 7.7 times that of individuals with CORT within normal values. This model was further improved by addition of an individual's 3-month stabilization score in block five (Fig 2D). The ASI psychological composite score narrowly fell outside of inclusion criteria ($p < 0.070$) and forced incorporation of this variable resulted in an apparently improved model ($\chi^2(2) = 8.97$, $p = 0.011$) but did not significantly change ($p = 0.074$) compared to that with abnormal CORT alone.

Collectively opioid addiction severity and both psychological and physiological stress assessments were observed to be necessary and sufficient to predict engagement and discontinuation risk during the initial six months of MMT.

4. Discussion

The present study set out to investigate whether an altered perception or physiological regulation of stress would negatively impact the methadone maintenance treatment (MMT) induction process and serve as a prognosticator of early (<6 month) discontinuation. First, we demonstrated that our treatment-seeking MMT population had increased stress, post-traumatic stress disorder (PTSD) symptoms, and abnormal cortisol (CORT) values, compared with previously published normative values and our internal control participants. Second, we discovered that increased perceived or PTSD-related stress (PSS14 or PCLC score), as well as abnormal CORT, predominated in non-completers and the same variables significantly contributed to MMT engagement measure outcomes. Within individuals who eventually discontinued treatment, greater withdrawal and ongoing opioid use also was observed throughout the first 6 months of the program. At 90 days post-admission the primary predictor of retention was a lower Addiction Severity Index (ASI) drug composite score with higher stabilization scores and the normative cortisol levels contributing, albeit without reaching statistical significance in our population. By 6 months abnormal cortisol alone was predictive of an individual discontinuing treatment. Longer-term MMT retention prognostications (at 6 months) also can be improved by inclusion of earlier (3-month) stabilization scores. The ASI psychological component closely approached criteria for final model inclusion and may be a beneficial tool as well. Overall, addiction severity impacts early discontinuation while an individual's ability to manage stress, especially physiologically, continues to negatively influence retention in MMT at 6 months.

This study was designed based upon the speculation that monitoring one dimension of stress may not be sufficient to discern an effect on recovery programs, as seen in previous work but anecdotally refuted in the clinic. The presented data replicated prior findings that neither perceived stress alone (Wasserman, Weinstein, Havassy, & Hall, 1998), nor independent PTSD diagnoses, reliably predict treatment retention (Hien et al., 2000; Himelhoch et al., 2012; Mills et al., 2007b). The data also expanded our understanding of which recovery goals are hampered by or impervious to these psychological stress anomalies. For instance, diagnostically high PTSD symptom severity improved attendance at group therapy during the initial 90 days of MMT but increased the relative risk of failure to stabilize by 6 months. Ongoing elevation of perceived stress was identified in non-completers and may have prognostic value that could not be identified in this limited population. Notably this study bolsters other recent work uncovering the vital influence of physiological HPA dysregulation on addiction treatment outcomes. The presence of higher peak CORT in response to induced stressors/cues in substance abuse dropouts by Daughters et. al. and Fatseas et. al. have indicated that a distorted HPA may exist in substance abusers (Daughters et al., 2009; Fatseas et al., 2011). In conjunction with the dissociated relationship observed in our study between abnormal CORT and elevated stress perception within non-completers, the breakdown of functionality within the physiological stress response system may underlie difficulties in managing the mental and physical challenges during recovery.

Consequently this may also explain the lack of significant psychologically centered relapse predictors identified to date. Further work is needed to elucidate the role of HPAA alterations in treatment-resistant opioid use and dependence; nevertheless, the findings of this study suggest salivary cortisol collection, which is an increasingly accessible laboratory service, and administration of the ASI at admission may help stratify relapse risk within the first 6 months of MMT.

Contributions to the knowledge of stress-related difficulties in MMT notwithstanding, this study is not without limitations. Individuals in MMT who did not participate in the study reported more past poly-drug use and legal problems on the ASI (Table. 1), as well as were more likely to discontinue treatment, produce fewer opioid-free UDS, and attend less requisite group therapy sessions. Therefore MMT clients who participated in the study may represent a more engaged population, such that undesirable discontinuation, persistent opioid use, and difficulties during initiation onto methadone may be underrepresented. Reliance upon self-report at intake might reflect over-reported distress of individuals trying to secure admission to the program, despite previous validation of this method in a heroin-dependent population (Mills, Teesson, Darke, & Ross, 2007a). Compliance of MMT study participants was another obstacle that hindered ongoing assessments and saliva sample collection during a focused time period. Although no association between time of collection or demographic variables was observed in singular CORT values within this study, there are documented inter-individual (Stone et al., 2001), racial (Skinner, Shirtcliff, Haggerty, Coe, & Catalano, 2011), hormonal (Roche, King, Cohoon, & Lovallo, 2013), and age-related (Ahn et al., 2007) differences in CORT distribution and diurnal rhythm. There is precedence for monitoring change from baseline CORT in substance abuse populations without assessment of circadian rhythmicity (Daughters et al., 2009; Fatseas et al., 2011; Fox et al., 2006), but future studies would be enhanced by investigating multiple salivary CORT samples over the course of the day. Although the difference between control and MMT study participant CORT values was significant, the study was underpowered to differentiate outcomes based upon abnormally low or high values separately. A causal relationship between stress, opioid dependence, and CORT value is beyond the scope of this study; nevertheless the combined categorical discrimination of irregularly elevated or blunted CORT had substantial prognostic implications in MMT discontinuation.

The duration of this study was chosen to concentrate on the initiation process for MMT due to known early difficulties in retention and intermittent withdrawal stress. Therefore the findings of the present study must be tempered with application to overall recovery success in opioid dependence treatment. Substance abuse is a chronic disease (T. A. McLellan, Lewis, O'Brien, & Kleber, 2000) that can require years of treatment to attain abstinence (Dennis, Scott, Funk, & Foss, 2005). In spite of this finding, the average length of stay in medication assisted treatment, such as MMT, was 197 days in 2008 with relapse rates that exceeded 50% due largely to drop out or administrative dismissal of noncompliant or violent individuals (Substance Abuse and Mental Health Services Administration, 2008). Considering the early risk of relapse and overdose (Cousins et al., 2011) and the exponential increase in mortality following drop-out (Gronbladh et al., 1990), identification of individuals vulnerable to stress-induced relapse as early as possible would be ideal.

The present study has ascertained that a combination of salivary CORT, PSS, ASI, and detailed drug severity (initiated opioid use on heroin or pills and amount of heroin/opioids used/day) measures could be used to recognize individuals that may benefit from adjuvant stress-reduction interventions. Dual diagnosis with concurrent treatment of PTSD and substance use disorder has demonstrated overall improvement in outcomes (Back, Waldrop, Brady, & Hien, 2006; Mills et al., 2012; Najavits, Weiss, Shaw, & Muenz, 1998), but broader application of stress amelioration techniques may be advantageous in this population. Mindfulness training, with or without integrated meditation, body relaxation, acupressure, or distress intolerance components, has shown stable decreases in subjective distress, basal cortisol, and the amplitude/duration of physiological reactivity to a stressor (cortisol response, heart rate), within healthy controls (Bottaccioli et al., 2014; Fan, Tang, & Posner, 2014) and tobacco (Davis, Manley, Goldberg, Smith, & Jorenby, 2014; Goldberg et al., 2014), cocaine (Brewer et al., 2009; Kevin W Chen, Berger, Gandhi, Weintraub, & Lejuez, 2013), or alcohol abuse (Stasiewicz et al., 2013) treatment cohorts. Increased abstinence behavior and decreased cravings have likewise resulted from mindfulness or neurofeedback (biofeedback focused on electroencephalograms, EEG) training in substance abuse treatment (Kevin W Chen et al., 2013; Goldberg et al., 2014; Ross, 2013; Stasiewicz et al., 2013), including opioid addiction (Dehghani-Arani, Rostami, & Nadali, 2013). Higher anxiety or distress has recently been found to increase willingness and perceived treatment efficacy for group stress reduction therapy in MMT (Barry et al., 2011), thus increasing feasibility of incorporating this training into existing intensive outpatient programs. The ASI drug and psychological composite scores with identification of abnormal salivary CORT could be used as routine admission screening tools to identify individuals susceptible to premature discontinuation and stratify treatment interventions in MMT. Assessing patient engagement and compliance again at three months may enable determination of interventional efficacy and predict ongoing retention or relapse-risk. Taken together, this study demonstrates the prevalence and importance of stress in MMT relapse and highlights risk stratification tools that could assist in development of a reduction in stress-induced relapse within opioid-dependent populations.

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Highlights

- Abnormal cortisol levels, elevated perceived stress and increased post-traumatic stress disorder symptoms are present in opioid-dependent individuals seeking treatment compared with controls or normative values.
- Six months after admission, methadone maintenance non-completers exhibit increased withdrawal symptoms, distress, and abnormal cortisol.
- Engagement in treatment, including attendance, opioid abstinence, and stabilization, can be predicted by perceived stress and drug severity assessed at admission.
- Premature discontinuation from methadone maintenance treatment is negatively influenced by drug severity at 3 months and the presence of abnormal cortisol by 6 months.

Figure 1. Stabilization score operationalized ongoing accomplishments in methadone maintenance treatment (MMT)

A) A participant's stabilization score was calculated by a combination of their opioid-free urine drug screens (UDS) and methadone dose stabilization status. Attainment of continuous opioid abstinence, as assessed by the first UDS each month, and maintaining a constant methadone dose for minimally four weeks surrounding the 90 or 185-day post-admission date were each worth one point, for a range of stabilization scores between 0–2. B) At three months nearly equal numbers of participants did not stabilize (i.e. maintain opioid-free monthly urines or obtain a consistent methadone dosage) or were partially stabilized (41.1%). By 6 months fewer participants partially stabilized (30.8%) and more fully stabilized (17.2 vs. 40.4%), while a smaller proportion of individuals remaining in treatment failed to maintain a constant methadone dose or opioid abstinence.

Figure 2. Survival curves demonstrate the impact of intake predictors on premature methadone maintenance treatment (MMT)

A–B) Kaplan-Meier analyses showed that higher stabilization scores are protective against MMT discontinuation, whereas inability to maintain a constant methadone dose and opioid abstinence accounts for nearly all dropouts, censored at 90 days (A, $X^2(2) = 9.488$, $p = 0.009$) or 185 days (B, $X^2(2) = 27.085$, $p < 0.001$). C) Kaplan-Meier analysis at six months showed that abnormal cortisol (values one standard deviation above or below the control cortisol range) resulted in decreased survival in MMT censored at 185 days ($X^2(1) = 5.418$, $p = 0.020$). D) Cox regression indicated that abnormal cortisol dominates prediction of discontinuation in MMT during the initial 6 months ($X^2(2) = 5.279$, $p = 0.022$, Abnormal CORT: $\text{Exp}(B) = 7.685$, $p = 0.052$).

Table 1

Group Differences in demographics, drug use history, and stress-related measures.

	Controls participants (n = 28)	MMT study participants (n = 58)	MMT non-participants (n = 49)	Normative Data	Statistic	p-value
Demographics						
Age	33.8 (SD = 10.2)	36.8 (SD = 9.7)	39.4 (SD = 9.3)	72.7% between 20–44 y.o. [†]	F(2, 134) = 3.026	0.052
Race (% Caucasian)	78.60%	63.80%	69.40%	Majority Caucasian [†]	X ² (4) = 2.465	0.651
Gender (% Female)	75.00%	48.30%	57.10%		X ² (2) = 5.504	0.064
Drug Use Characteristics						
Age of 1st Opioid	--	22.5 (SD = 8.5)	22.9 (SD = 8.9)		t(105) = -0.248	0.804
Type of 1st Opioid (% heroin)	--	48.30%	63.30%		X ² (1) = 2.143	0.12
Percent Never used Heroin	--	6.90%	4.10%		X ² (1) = 0.398	0.528
Opioid use duration (years)	--	10.4 (SD = 9.8)	13.6 (SD = 10.0)		t(105) = -1.261	0.21
Am't of Heroin (bags/day) used	--	7.5 (SD = 4.7)	7.5 (SD = 8.4)		t(105) = -0.003	0.997
IVDU (% yes)	--	58.60%	55.10%		X ² (1) = 0.134	0.714
Past poly-drug use (% yes)	--	84.50%	98.00%		X ² (1) = 5.694 [*]	0.017
ASI (scale 0–1): medical	--	0.30 (SD = 0.26)	0.27 (SD = 0.27)		t(101) = 0.634	0.528
ASI (scale 0–1): employment	--	0.91 (SD = 0.16)	0.93 (SD = 0.13)		t(101) = -0.738	0.462
ASI (scale 0–1): legal	--	0.04 (SD = 0.09)	0.10 (SD = 0.16)		t(64.067) = -2.236 ^{*,†}	0.021
ASI (scale 0–1): alcohol	--	0.03 (SD = 0.11)	0.04 (SD = 0.10)		t(101) = -0.071	0.943
ASI (scale 0–1): drugs	--	0.36 (SD = 0.08)	0.37 (SD = 0.09)		t(101) = -0.416	0.678
ASI (scale 0–1): social	--	0.12 (SD = 0.13)	0.12 (SD = 0.10)		t(101) = 0.182	0.856
ASI (scale 0–1): psychological	--	0.34 (SD = 0.21)	0.32 (SD = 0.20)		t(101) = 0.439	0.662
Stress-Related Measures						
Perceived Stress Scale (PSS-14) Scores	22.93 (SD = 8.36)	30.78 (SD = 8.32)	--	19.62 (SD = 7.49) [‡]	F(2,2436) = 63.74 ^{*,‡}	<0.001
PSS-14 Score > 1 SD above norms (%)	32.10%	72.50%	--		X ² (1) = 13.09 [*]	<0.001
PSS-10 Score (throughout treatment)	--	18.78 (SD = 6.00)	--	13.02 (SD = 6.35) [‡]	t(2390) = 5.48 [*]	<0.001
PTSD Checklist-Civilians (PCLC) Scores	28.74 (SD = 12.64)	48.62 (SD = 15.59)	--		t(79) = 5.441 [*]	<0.001

	Controls participants (n = 28)	MMT study participants (n = 58)	MMT non-participants (n = 49)	Normative Data	Statistic	p-value
PCLC Score diagnostic of PTSD (% >44) [‡]	13.00%	58.60%	--		$\chi^2(1) = 13.787^*$	<0.001
Cortisol (CORT, nmol/L)	4.39 (SD = 2.00)	6.12 (SD = 4.08)	--	11AM: 4.69; 4PM: 2.48	$t(74.995) = -2.26^{*†}$	0.014
Abnormal Cortisol (%)	25.0%	60.0%	--			

* Significant difference ($p < 0.05$)

[†] Welch's t-test was performed with pooled variance due to a significantly different variance detected by Levene's test

[‡] Post-hoc Tukey analysis demonstrated no difference between Cohen's normative population and our controls although both were significantly different than MMT individuals

References:

- ¹ (SAMHSA, 2013),
- ² (Cohen and Williamson, 1988),
- ³ (Blanchard et al., 1996),
- ⁴ (Salimetrics Cortisol ELISA kit insert)

Table 2

Stress and outcome differences between MMT completers and non-completers by 185 days

	Completers (n = 44)	Non-completers (n = 14)	Statistic	p-value
Stress-Related Measures				
PSS-14 at intake	30.05 (SD = 8.75)	33.07 (SD = 6.56)	$t(56) = -1.190$	0.239
Average PSS-10 during treatment	18.0 (SD = 5.67)	24.38 (SD = 6.52)	$t(35) = -2.080$	0.045*
PCLC raw score	48.8 (SD = 16.0)	47.9 (SD = 14.6)	$t(56) = 0.189$	0.851
PTSD diagnosis likely (PCLC > 44)	43.20%	35.70%	$X^2(1) = 0.244$	0.621
Abnormal CORT (present)	51.3%	90.9%	$X^2(1) = 5.614$	0.018*
Withdrawal Symptoms (COWS)	7.55 (SD = 3.48)	10.56 (SD = 4.32)	$t(40) = -2.104$	0.042*
Engagement Measures				
Self-reported Days used Opioids per week	1.90 (SD = 2.07)	4.56 (SD = 1.42)	$t(35) = -2.485$	0.018*
Medication Compliance > 95%	68.20%	21.40%	$X^2(1) = 9.466$	0.002**
Group therapy attendance (%)	68.2% (SD = 20.9%)	47.7% (SD = 32.4%)	$t(56) = 2.769$	0.008**
Level of % total opioid-free UDS	1–43.2%, 2–22.7%, 3–24.1%	1–78.6%, 2–21.4%, 3–0.0%	$X^2(2) = 7.352$	0.025*
Stabilization of care Score	0–29.5%, 1–47.7%, 2–22.7%	0–78.6%, 1–21.4%, 2–0.0%	$X^2(2) = 11.126$	0.004**

*
p < 0.05,**
p < 0.01

Table 3

Survival analyses at three and six months post-admission into MMT

	Model Fit Characteristics	Significant Predictors	Interpretation
3-month Survival			
Linear Regression of Days in MMT (cens. at 90)	adjR ² = 0.101, p = 0.014	ASI Drug: B = -62.278, p = 0.014	↑ Drug Severity ↓ Number of Days stayed in MMT
Binary Logistic Regression of End MMT by 90 days (y/n)	pseudoR ² = 0.185, p = 0.042	ASI Drug: B = 12.493, p = 0.055	↑ Drug Severity ↑ Risk of early discharge
Kaplan-Meier with Stabilization Score	X ² (2) = 9.488, p = 0.009	All 6 non-completers had a stabilization score = 0	Methadone dose stabilization and Opioid Abstinence ↓ Relapse Risk
Kaplan-Meier with Abnormal CORT category	X ² (1) = 2.807, p = 0.094	4 non-completers with saliva all had abnormal CORT	Abnormal CORT may negatively impact retention in MMT by 90 days
Cox Regression with intake predictors	X ² (1) = 4.845, p = 0.028	ASI Drug: Exp(B) = 92795, p = 0.036	Only ↑ Drug Severity reliably ↑ Relapse Risk prior to 90 days
6-month Survival			
Linear Regression of Days in MMT (cens. at 185)	adjR ² = 0.055, p=0.059	PSSxCORT: B = -0.736, p = 0.059	↑ Stress in clients with abnormal CORT may ↓ Number of Days stayed in MMT
Binary Logistic Regression of End MMT by 185 days (y/n)	pseudoR ² = 0.189, p=0.010	Abnormal CORT: B = 2.626, p = 0.022	Abnormal Cortisol ↑ Risk of discharge
Kaplan-Meier with Stabilization Score	X ² (2) = 27.085, p < 0.001	13 non-completers had a stabilization score = 0; 14th had score = 1	Methadone dose stabilization and Opioid Abstinence ↓ Relapse Risk
Kaplan-Meier with Abnormal CORT category	X ² (1) = 5.418, p = 0.020	10 of 11 non-completers with saliva had abnormal CORT	Abnormal CORT negatively impacts retention in MMT
Cox Regression with intake predictors	X ² (2) = 5.279, p = 0.022	Abnormal CORT: Exp(B) = 7.685, p = 0.052	Abnormal Cortisol ↑ Risk of Relapse
Cox Regression with intake predictors + 3mo. Stabilization	X ² (4) = 10.006, p = 0.019	Abnormal CORT: Exp(B) = 5.963, p = 0.096	Stabilization score from 3mo. may improve prediction of retention
Cox Regression with intake predictors + 3mo. Stabilization	X ² (4) = 10.006, p = 0.019	Stabilization Score = 0: Exp(B) = 48332, p = 0.933	Stabilization score from 3mo. may improve prediction of retention
Cox Regression with intake predictors + 3mo. Stabilization	X ² (4) = 10.006, p = 0.019	Stabilization Score = 1: Exp(B) = 23375, p = 0.938	Stabilization score from 3mo. may improve prediction of retention