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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 and 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.

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; McLellan, Luborsky, Woody, O'Brien, & Druley, 1983). International reports demonstrate that the prevalence of affective disorders within substance abusers is between 30 and 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, 2007) 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

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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 (Ferrari, Coccia, Bertolini, & Sternieri, 2004; National Institute on Drug Abuse., 2012). 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; 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, Gilabert, 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 (Bearn et al., 2001; Cami et al., 1992). 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, & Gunne, 1990; 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 & Mental Health Services Administration, S. A. a. M. H. S, 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 HPAA 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