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Editorial Open Access

Prescription Opioid and Stress

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Editorial

Stress is a well-known risk factor for the development of drug addiction and relapse [1]. There is evidence in the literature that chronic psychosocial stress originated in childhood negatively influences ventral striatum response to reward [2,3], and such reward dysfunction underlies symptoms of depression [4], anxiety [5], and post-traumatic stress disorder (PTSD) [6]. Chronic psychosocial stress increases the risk of developing substance use disorders (SUDs) by significantly altering the brain's stress circuits and their communication with the mesocorticolimbicstriatal (MLS) dopamine pathway responsible for stress regulation and reactivity, reward, craving, memory, and decision making [7]. In addition, previous studies have indicated that chronic alcohol and drug use including opioid use results in neuroplasticity in the brain's stress pathways and its pathophysiology with reward circuitry [8-10], again highlighting the importance of studying this MLS pathway in SUDs. Based on earlier studies, both stress-related affective disorder (SAD; anxiety, depression, PTSD) and opioid addiction affect the same regions, such as insula, ventral striatum, hippocampus, amygdala, anterior cingulate cortex, and prefrontal cortex [11-15] within the MLS pathway. These regions cover the network related to drug cue processing (DCPN) involving the MLS pathway that Ray, the first author of this brief communication and her colleagues recently identified [16], which mediates cognitive and affective aspects of addiction.

Earlier studies have suggested that acute psychosocial stress can come from recent past, current, or anticipated demands on the individual and has been associated with greater relapse risk for individuals with cocaine, alcohol and nicotine use disorders [10,17,18]. Additionally, neural mechanisms underlying acute stress and/or drug cue processing have been studied in alcohol, nicotine, and cocaine users by utilizing functional magnetic resonance imaging (fMRI) technique [10,19-22]. For example, acute stress and alcohol-cue exposure has been associated with an increased activity in some regions within the MLS circuit in social drinkers [21]. In addition, corticostriatal-limbic hyperactivity appears to be linked to stress cues in women, drug cues in men, and neutral-relaxing conditions in both men and women among cocaine-dependent individuals [20]. In animal literature, acute stress has been associated with increased self-administration of cocaine and amphetamine and reinstatement of cocaine seeking *via* activation of the mesocorticolimbic dopamine system [23]. Thus, although how stress is related to drug use is fairly well established, whether the same applies to prescription (PO) use is poorly understood. This topic is currently one of the National Institute on Drug Abuse's (NIDA) priority research areas.

Few studies have examined a relationship between stress and PO use [24-26]. PO abuse is a critical health problem in the U.S. and internationally [27]. There were 18,893 overdose deaths related to PO pain relievers in 2014 alone [28] and the costs of the U.S. PO epidemic are estimated at $78.5 Billion [29] and rapidly increasing with increasing PO abuse. From 2002 to 2011 there was a 1.9-fold increase in the total number of deaths involving POs [30]. A recent study by Feingold et al. [31] on patients receiving PO for pain showed that 75.3% of patients with severe depression and 50% of those with mild to moderate anxiety misuse PO, and that patients with moderate to severe depression were significantly more likely to screen positive for severe anxiety as well. In addition, Fareed and colleagues (2013) reported that 33% of opioid users have a concurrent PTSD. Therefore, there is a strong association between SAD and PO abuse. Acute stress may disrupt the regulation of craving and emotions for PO users. By the same token, when treated with lofexidine, α2A adrenergic receptor agonist, opioid-dependent (PO and heroin) individuals in treatment decreased stress-induced and cue-induced opioid craving [26], suggesting that opioid abstinence can be improved. Unfortunately, there is very little research on neural pathways affected by chronic and acute stress among PO users and virtually nothing is known about how chronic and acute stress affect the PO recovery trajectories at the behavioral, physiological, and neural levels for individuals in treatment. The PO addiction field can be advanced by utilizing experimental functional magnetic resonance (fMRI) studies that will assist the development of more effective and precise treatment strategies for PO users. Specifically, there is a need to examine how PO users with a current diagnosis of SAD (PO+SAD group) in inpatient treatment differ from PO users in treatment without SAD (PO-SAD group) in brain structure, function, craving, as well as in their ability to respond to acute psychosocial stress [32].

We further suggest that the PO addiction field may be further benefited by utilizing innovative Machine Learning (ML) computational algorithms that can serve as predictive models of PO recovery and elucidate neural signatures associated with recovery in PO+SAD and PO-SAD groups using neural features from DCPN as well as clinical, behavioral and physiological features, for example, cortisol level. ML is now widely utilized to reveal hidden patterns in various human behavior and medical conditions for more accurate diagnosis and better treatment prediction. Especially in brain research, ML algorithms, when carefully designed, may identify the malleable intermediate phenotypes between therapies and the underlying neuropathophysiology.

The first author Ray would next like to undertake the research activities that have been identified as the research needs in the PO addiction field by the authors of this communication. This research

will be instrumental for promoting a biologically-based prediction of treatment prognosis, and ultimately improving the precision of the available interventions for individuals with co-occurring opioid/other SUDs and SADs.

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