INFLUENCE OF EXERCISE ON OPIOID WITHDRAWAL

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INFLUENCE OF EXERCISE ON OPIOID WITHDRAWAL

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ABSTRACT

Opioids are a class of drug normally associated with analgesia (reduced pain) (Chahl, L., 1996). In other words, when an opioid activates mu opioid receptors, it can result in an analgesic response. Unfortunately, it is also known to produce dependence in some patients. Dependence can also lead to unwanted side effects such as withdrawal. Treating dependence can be challenging because of the discomfort of withdrawal. This study evaluated if exercise such as running, can help decrease the severity of withdrawal, after the animals have developed a tolerance to the opioid. This project is trying to mediate the strength of withdrawal. Research has linked physical activity to improvements in cognition and overall brain function in the human body (Hillman, et al., Kramer, 2008). Non-human animal model allows access to causal mechanisms of whether exercise can reduce opioid tolerance in general. If exercise can reduce symptoms of withdrawal, it can inform clinical models and treatment facilities managing patients with opioid abuse.

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INTRODUCTION

Opioids are among the most commonly abused drugs in the United States (Eisch, Barrot, Schad, Self, & Nestler, 2000). Opioid prescriptions have increased dramatically over the past 20 years and opioids such as oxycodone (Oxycontin), morphine and hydrocodone have become increasingly popular (Drewes, Jensen, Nielsen, Droney, Christrup, Arendt-Nielsen, Riley & Dahan, 2012). In the United States, medical use of opioids increased 400% between 1996 and 2000 (Gallego, Baron, & Arranz, 2007). At present, 86% of the market consists of four opioids: controlled-release hydromorphone, controlled-release morphine, controlled-release oxycodone and transdermal fentanyl (Gallego, Baron, & Arranz, 2007). Opioids' ability to produce profound delight and their ability to abolish pain has ignited the mind of humans for years (Mehendale, Goldman, Mehendale, Rana, 2013). Examining opioids and their use in the light of scientific knowledge, is clear that the history of opioid use is littered with the comparison of originality, anticipation, satisfaction, scientific progress and social disappointment (Mehendale, et al., 2013).

When used properly, opioids have the capacity to relieve pain and discomfort, but when used improperly (opioid use that is not medically authorized), it can cause overdose, dependence or tolerance, addiction, and sometimes death (Mehendale, et al, 2013). These drugs act by binding to opioid receptors in the body and block the transmission of pain messages to the brain (Mehendale, et al., 2013). Used correctly, opioids are helpful for people suffering from chronic pain or pain from surgery.

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Unrelieved pain due to surgery, trauma, cancer or even noncancer related conditions, continues to be a major public health concern (Joranson, et al., 2000). Even though there are many nonpharmacologic medications such as acupuncture, therapy, relaxation techniques etc, that can be used for pain relief, opioids such as oxycodone, are the basis of pain management (Joranson, et al., 2000). Opioids can have a high abuse rate, making it regulated under international and national narcotics abuse and controlled substance laws (Joranson, et al., 2000). These laws try to serve a dual purpose at allowing proper treatment and care for those suffering from pain or discomfort, all while preventing these substances from become misused and abused (Joranson, et al., 2000). Health care providers are reluctant to prescribe, administer or dispense opioids to patients, due to the possibility of addiction or misuse (Joranson et al., 2000).

Dependence/Tolerance

Drug addiction/misuse can be described as a chronic, relapsing disorder characterized by compulsive drug seeking, all the while knowing the harmful consequences, and long-lasting changes in the brain the drug can do (National Institute on Drug Abuse, 2018). Professionals try to avoid using the word addiction and instead use, tolerance, dependence or misuse (National Institute on Drug Abuse, 2018). The difference between addiction and tolerance is, tolerance is the need to take higher doses of a drug to get the same effect (National Institute on Drug Abuse, 2018). It often accompanies dependence, and it can be difficult to distinguish the two.

Dependence can occur with the regular (daily or almost daily) use of any substance, legal or illegal, even when taken as prescribed (National Institute on Drug Abuse, 2018). It

occurs because the body naturally adapts to regular exposure to a substance (prescription drug) (National Institute on Drug Abuse, 2018). When that substance is taken away, symptoms can emerge while the body re-adjusts to the loss of the substance (National Institute on Drug Abuse, 2018). Physical dependence can lead to craving the drug to relieve the withdrawal symptoms (National Institute on Drug Abuse, 2018; Siegel, 2008). Opioids are increasingly being misused (Trivedi, Shaikh, & Gwinnut, 2007). This behavior of misuse can lead to addiction or possible overdose (Trivedi, Shaikh, et al., 2007). A defining characteristic of addiction is the appearance of drug withdrawal symptoms when drug use terminates (Siegel, Ramos, 2002). These symptoms may occur long after the last drug administration and may be one reason for relapse (Siegel, Ramos, 2002). A drug that mediates these symptoms would be a useful addiction treatment tool (Siegel, Ramos, 2002).

Chronic drug administration may influence the addiction process of the body by developing a dependence to a certain drug, which can result in withdrawal behavior (Robbins & Everitt, 1999). It is important to understand how addiction works at the behavioral, cognitive and neuropsychological levels (Robbins & Everitt, 1999). Drug-seeking behavior can become powerfully associated with environmental cues, which, as conditioned stimuli, predict not only the availability of drugs and their associated hedonic (pleasant or unpleasant) effects, but also aversive withdrawal states (Robbins & Everitt, 1999).

Many drugs that support compulsive self-administration will produce some type of dependence when the drug is withdrawn (Tiffany, 1990). Withdrawal symptoms include, anhedonia (inability to feel pleasure), negative affect, and craving (Bock, 1999). Opioid withdrawal symptoms often include restlessness, insomnia, vomiting, muscle and bone pain,

diarrhea and cold flashes (National Institute on Drug Abuse, 2007). Relief from these symptoms is believed to be a major factor that motivates drug use (Bock, 1999). Patients who have been prescribed an opioid for pain management and take the drug for two or more weeks, often report experiencing withdrawal symptoms when the drug is discontinued (Wakim, 2012).

At the cellular level, opioids work by activating opioid receptors (Trivedi, Shaikh, et al., 2007). Naturally occurring opioid compounds are found in plants and produced in the body (endogenous opioids), where they are distributed throughout the central nervous system (CNS) (Trivedi, Shaikh, et al., 2007). These endogenous compounds are peptides that have variable potency and are preferentially bound by different opioid receptors; mu, kappa and delta receptors (Trivedi, Shaikh, et al., 2007). They have numerous actions including modulation of pain and control of the cardiovascular system, particularly in shock (Trivedi, Shaikh, et al., 2007). Although of interest to pharmacologists, endogenous opioids currently have no clinical role (Trivedi, Shaikh, et al., 2007). Synthetic and semi-synthetic opioids are widely used clinically, primarily for their analgesic actions (Trivedi, Shaikh, et al., 2007).

When an opioid such as oxycodone or morphine binds to one of these receptors, this leads to a conformation change (Trivedi, Shaikh, et al., 2007). Effects of a conformational change regarding receptor sites, can be closing of calcium channels, stimulation of potassium efflux leading to hyperpolarization and reduced cyclic adenosine monophosphate production (Trivedi, Shaikh, et al., 2007). This means there is a reduction in neuronal cell excitability, that in turn results in reduced nociceptive (pain) impulses (Trivedi, Shaikh, et al., 2007).

Opioids such as oxycodone and morphine can cause initial feelings of pleasure by acting on the natural reward system in the brain (National Institute on Drug Abuse, 2007).

Oxycodone

Morphine has traditionally been the recommended choice of strong opioid for pain (Drewes, et al., 2012). In recent years, there has been growing availability of other alternative strong opioids, including, oxycodone, buprenorphine, hydromorphone, methadone, alfentanil and fentanyl (Drewes, et al., 2012). Previous behavioral studies looking at rats, compared oxycodone to morphine and found significantly weaker and briefer antinociception (reduced sensitivity to pain) in the tail flick and hot plate tests after intrathecal and intracerebroventricular administration (Kalso, 2005). Opioids are prescribed mainly to relieve pain symptoms, but they can have negative effects including drowsiness and physical dependence (Rapeli, et al., 2006). Over the past 10 years, there has been a resurgence of interest in the role of urges and cravings in physical dependence (Tiffany, 1990).

Pharmaceutical companies introduced new formulations, such as extended release oxycodone (OxyContin), which were frequently prescribed because of a presumed lower likelihood of abuse, while in fact, were heavily abused (Jones, Viswanath, Peck, Kaye, Gill, & Simopoulos, 2018). Today oxycodone is mainly used as controlled-release tablets (drug is released slowly after ingestion) for chronic pain (Kalso, 2005). However, both morphine and oxycodone provide effective analgesia in acute and chronic pain (Kalso, 2005). Oxycodone has a more favorable pharmacokinetic profile (Kalso, 2005).

Oxycodone's oral (ingested) bioavailability (substance entered into the system to have an active effect) is significantly higher and therefore the individual variation in

bioavailability and expected plasma concentrations is less (Kalso, 2005). This variation means that the higher effect a compound has on an individual's system, the more that drug is binding to its proper receptors, rather than free flowing throughout the body, creating lower plasma concentration (Kalso, 2005). Specifically, after oral administration, its bioavailability in humans is between 60 and 87% and its elimination half-life is 3–5 hours (Kummer, Hammann, Moser, Schaller, Drewe & Krahenbuhl, 2010; Gallego, Baron, & Arranz, 2007).

Oxycodone has an analgesic potency similar to morphine and reveals affinity primarily for μ-opioid receptors (Kummer, et al., 2010). Clinical analgesia commences within one hour and in the controlled-release formulation, analgesia lasts for twelve hours (Gallego, et al., 2007). Oxycodone is heavily metabolized, with less than 10% of the orally administered drug expelled in urine (Kummer, et al., 2010).

Both oxycodone and morphine cause typical opioid-related effects such as, the activation of the natural endogenous opioid system (Kalso, 2005). However, several reports indicate that oxycodone causes fewer hallucinations (Kalso, 2005). Less itching with oxycodone may be related to the fact that oxycodone leads to significantly less histamine being released than morphine (Kalso, 2005). Oxycodone penetrates easily into interstitial space and inside cells because of its relatively low molecular weight and its lipophilic nature (chemical compound being able to dissolve in fats, oils, lipids etc) (Gallego, et al., 2007). A high percentage of the drug remains outside the vascular compartments and is not eliminated by the kidneys or the liver, which contributes to its slow release (Gallego, et al., 2007). The antagonistic effects of oxycodone are those that are typically found in opioids (Gallego, et al., 2007).

Withdrawal

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) criteria, signs and symptoms of opioid withdrawal include lacrimation (flow of tears) or rhinorrhea (nasal cavity is filled with a significant amount of mucus fluid), diarrhea, nausea/vomiting, pupillary dilation and photophobia (intolerance of light), insomnia, autonomic hyperactivity (tachypnea, hyperreflexia, tachycardia, sweating, hypertension, hyperthermia), and yawning (Shah, Huecker, 2019). Rate and intensity of these side effects tend to decrease in the course of time, as is the case for other opioids (Shah, Huecker, 2019).

When opioid withdrawal signs are present, pharmacological management of opioid withdrawal is done by one of the following; gradual cessation of an opioid agonist (methadone), short-term use of a partial mu-opioid agonist (buprenorphine), or detoxification using opioid antagonists (naltrexone and naloxone) (Shah, Huecker, 2019). Naltrexone or more commonly known as Naloxone, is one of the most prescribed opioid antagonists for opioid abusers (Shah, Huecker, 2019). Naloxone dislodges an opioid from its binding site, causing a detox in the body (Chartoff, Carlezon, 2014). This detoxification process is a necessary step in treating opioid dependence (Chartoff, Carlezon, 2014). When the body goes through a detox from drugs such as opioids, it can be uncomfortable and very stressful (Chartoff, Carlezon, 2014). Abusers dependent on a substance, quickly learn the most effective way to stop the negative side effects of withdrawal, is to administer the drug again (Chartoff, Carlezon, 2014).

Both acute drug administration and stress elicit states of arousal and engage many of the same neural circuits (Koob, 2008). Both activate the HPA axis, (hypothalamic-pituitary-

adrenal axis) which result in release of stress hormones and peptides (corticosterone, glucocorticoids, endogenous opioids) (Koob, 2008). Corticosterone can enhance dopamine release, which is one of the main pathways activated when drug of abuse is administered (Chartoff, Carlezon, 2014). Over time, when abusers have become dependent on a drug, the withdrawal results in activation of that HPA stress response, causing distress and discomfort (Chartoff, Carlezon, 2014). Understanding the neurobiology behind opioid withdrawal is a key factor to help clinicians develop a proper treatment plan for those seeking help (Chartoff, Carlezon, 2014).

Exercise/Benefits

Physical activity, specifically exercise, has been suggested as a potential treatment for drug addiction/abuse and a method of mediating withdrawal symptoms (Bock 1999; Lynch, et al., 2013). Exercise and behavioral enrichment paradigms, such as environmental enrichment, rehabilitation training, and learning, affect different factors within the brain, including regulation of growth factors, neurogenesis, structural changes, brain derived neurotrophic factors and even protect against apoptosis (cell death) (Cotman & Berchtold, 2002).

Exercise has demonstrated substantial benefits in terms of mental and physical health with improvements in cardiovascular health and health-related quality of life, and reduction in the risks for various chronic diseases (type-2 diabetes, coronary heart disease, obesity) (Weinstock, Wadeson, VanHeest, 2012). Exercise also has well-established beneficial effects on reducing symptoms of anxiety, lowering the risk of major depression relapse, decreasing urges to drink alcohol, and lessening nicotine withdrawal and cannabis and cigarette cravings

(Weinstock, et al., 2012). Additionally, exercise has greater benefits as a means of coping and managing depression than other substance-free activities. (Weinstock, et al., 2012). The benefits of exercise are abundant for mental and physical health, which is why exercise is recommended as an alternative treatment over other health methods (Weinstock, et al., 2012).

Given the benefits noted, exercise has also harbored attention to the mechanism of action it brings to patients struggling with substance abuse (Weinstock, et al., 2012). Possible mechanisms could be, increased socialization, emotional regulation, decreased anxiety, improving management to stress etc. (Weinstock, et al., 2012). It has been noted, those that use substances to self-medicate or avoid negative stimuli, could be using a drug as an alternative to the emotion, stress, anxiety, depression etc, that they are facing (Weinstock, et al., 2012). Opioids impact the brains natural reward pathway by releasing powerful neurotransmitters, eliciting feelings of pleasure (Weinstock, et al., 2012). Since the human body, has a natural endogenous opioid system, research has shown, exercise can release those endogenous opioids in the central and peripheral nervous system, resulting in that sense of pleasure and reward that a compound would (Weinstock, et al., 2012). Dopamine is a natural neurotransmitter in the body that is released during pleasure/reward (Greenwood et al., 2011; MacRae et al., 1987).

Expanding on the neurobiological process of what exercise does, aerobic exercise stimulates the release of endogenous opioid peptides and increases the nociceptive (pain) threshold in a naloxone-reversible manner (Greenwood et al., 2011; MacRae et al., 1987). Mechanistically, physical activity and exercise activate the same reward pathway. This is the same reward pathway as drugs of abuse (mesolimbic pathway), through increases in

dopamine concentrations and dopamine receptor binding (Greenwood et al., 2011; MacRae et al., 1987).

Physical exercise can lead to activation of serotonin networks as well as dopaminergic networks (Greenwood et al., 2011; MacRae et al., 1987). As mentioned, when an opioid is administered in the body, not only does it block pain receptors, but it activates that dopamine/mesolimbic pathway, creating feelings of pleasure (Greenwood et al., 2011; MacRae et al., 1987). Endogenous opioids have chemical properties similar to that of opioids such as oxycodone and morphine, which potentially makes exercise a compatible substitute for drug abuse (Weinstock, et al., 2012; Lynch, et al., 2013).

By the early 1990s, converging evidence suggested that many drugs of abuse act through mechanisms involving the brain neurotransmitter dopamine and different neural structures, including: the nucleus accumbens, ventral tegmental area, amygdala and prefrontal cortex (Robbins & Everitt, 1999). During exercise, sensitivity to the antinociceptive (blocking the detection of a painful stimulus) effects of mu opioids decreases, providing support that exercise may lead to the development of resistance to administered opioids (Smith & Lyle, 2006). Running has been shown to alter the levels of endogenous opioids in different regions of the rat brain (Boone, 1996; Werme, Thoren, Olson, & Brene, 2000). Evidence for the role of the opioid system on the effects above is also derived from studies demonstrating that the opioid antagonist naloxone prevents elevation of the nociceptive threshold following exercise in normal subjects (Droste, Greenlee, Schreck, & Roskamm, 1991).

While opioid antagonists are an effective intervention for opioid dependence, there is room for improvement, as patients continue to abuse other substances (Weinstock, et al., 2012). If exercise was introduced in a productive manner, considering all the risks, clinicians could have a possible treatment plan for opioid/drug abusers to slowly get their bodies, back to homeostasis (Weinstock, et al., 2012).

Treatment Approaches

The path to drug abuse/addiction begins with the voluntary act of taking drugs. Over time, a person's ability to choose not to do so becomes compromised (National Institute on Drug Abuse, 2019). Seeking and taking the drug becomes compulsive (National Institute on Drug Abuse, 2019). This is mostly because of long-term drug exposure on brain function (National Institute on Drug Abuse, 2019). Addiction affects parts of the brain involved in reward and motivation, learning and memory, and control over behavior, such as low resistance to a drug, violence, personality changes etc. (National Institute on Drug Abuse, 2019). People cannot simply stop using drugs for a few days and be cured. Most patients need long-term or repeated care to stop using completely or slowly get back to homeostasis and recover their lives (National Institute on Drug Abuse, 2019).

There are many options that have been successful in treating drug addiction, including, behavioral counseling, medication, medical devices and applications used to treat withdrawal symptoms (National Institute on Drug Abuse, 2019). Other options include evaluation and treatment for co-occurring mental health issues such as, depression and anxiety and long-term follow-up to prevent relapse (National Institute on Drug Abuse, 2019).

Medications help suppress withdrawal symptoms during detoxification (National Institute on Drug Abuse, 2019). Detoxification is not in itself treatment, but only the first step in the process (National Institute on Drug Abuse, 2019). Patients who do not receive any further treatment after detoxification usually resume their drug use (National Institute on Drug Abuse, 2019).

Acting on the same targets in the brain as oxycodone and morphine, methadone and buprenorphine suppress withdrawal symptoms and temporarily relieve cravings (National Institute on Drug Abuse, 2019). Naltrexone (Naloxone) blocks the effects of opioids at their receptor sites in the brain (National Institute on Drug Abuse, 2019). Some medications help patients reduce drug seeking and related behavior and help them become more open to behavioral treatments (National Institute on Drug Abuse, 2019). When determining treatment for those undergoing opioid abuse, it is vital to understand each individual patient (NIDA, 2020). Men and woman can be different in determining treatment due to the different responsive behavior (NIDA, 2020).

Some research indicates that women are more sensitive to pain than men and more likely to have chronic pain, which could contribute to the high rates of opioid prescriptions among women of reproductive age (NIDA, 2020). In addition, women may be more likely to take prescription opioids without a prescription to cope with pain, even when men and women report similar pain levels (NIDA, 2020). Research also suggests that women are more likely to misuse prescription opioids to self-treat for other problems such as anxiety or tension (NIDA, 2020). However, from 1999 to 2016, deaths from prescription opioid

overdoses increased more rapidly for women (596 percent) than for men (312 percent) (NIDA, 2020).

Although agonist maintenance therapies produce better outcomes for most opioid addicts, they continue to seek opioid withdrawal primarily to lower the cost of their habit or as pretreatment before the therapeutic community or opioid antagonist maintenance (Kleber, 2007). High relapse rates are probably less a meaning of withdrawal method and due more to reasons for seeking detoxification, post withdrawal treatment, or brain changes developed during dependence maintenance (Kleber, 2007). Due to previous research, treatment centers approach patients with many different options (Kleber, 2007). As mentioned, there are the agonist medications, therapy, counseling, rehabilitation etc. (Kleber, 2007). Withdrawal from opioids is uncomfortable and does cause various health problems (Kleber, 2007). Clinicians have seen treatment currently used in institutions as being effective for an acute amount of time (Kleber, 2007). One treatment that is not explored enough is the option of exercise as a treatment for withdrawal (Kleber, 2007).

Previously mentioned, exercise has shown many physiological and physical benefits on the body (Weinstock, et al., 2012). If there was a way to use exercise as a treatment for patients undergoing withdrawal, that should be further explored (Weinstock, et al., 2012). Exercise's production of dopamine can help addicted individuals find other non-substance-related hobbies to manage long-term recovery (Elevate Addiction Services, 2018). Some addiction recovery centers have even pushed for the implementation of opiate-recovery-centric gymnasiums (Elevate Addiction Services, 2018). Easy exercise equipment access, they suspect, may promote the physical activity needed to combat acute and post-acute

withdrawal symptoms (Elevate Addiction Services, 2018). The act of practicing an exercise routine, and committing to a physical activity, can keep the mind off drug use, too (Elevate Addiction Services, 2018). Exercise during opiate withdrawal is surprisingly similar to traditional treatment methods (Elevate Addiction Services, 2018). Exercise is still being explored in depth and how to properly treat patients with exercise, if that is the diagnosis being prescribed (Weinstock, et al., 2012). Research has shown multiple benefits of exercise and if it can alleviate withdrawal symptoms in those struggling with addiction, there needs to be a harder push and more awareness for treatment centers to offer (Weinstock, et al., 2012).

Purpose/Hypothesis

The purpose of this project is to evaluate whether exercise will mediate withdrawal symptoms in opioid-dependent female rats. The goal of which would be to potentially inform clinical models of the role exercise may have in treating opioid withdrawal aversion.

METHOD

Animals and Housing

Two cohorts of 20 mature Sprague Dawley female rats of 4 months (18 weeks, full growth) were ordered from Envigo and transported to the Jackson Street Laboratory. Female rats were chosen because female rats do not receive enough credit in biomedical research (Wizemann and Pardue, 2001). This is often on the assumption that results from males apply to females, or because of concern that hormonal cycles decrease the equality of study populations and confound effects of experimental manipulations (Wizemann and Pardue, 2001).

Rats were housed in a semi-self-contained housing system (Optirat©) two to each cage and given standard rodent chow and hard-wood chip (sani-chip) bedding. The rats were also given unrestricted access to food and water. The vivarium was maintained on a recommended 12-hour light/dark cycle (Miladi-Gorji, Rashidy-Pour, & Fathollahi, 2011).

Rats in the age range from around 28–42 days are often hyperactive and exhibit greater exploration in novel situations than other aged rats (Spear, 2000). They also frequently appear hyper-reactive to stimuli (high sensitivity), displaying substantially greater startle response amplitude than adults (Spear, 2000). Using rats 18 weeks of age, allow for a more reliable comparison with human primates undergoing drug abuse according to NIH. Young adults (age 18-25) are the biggest abusers of prescription opioid pain relievers (National Institute on Drug Abuse, 2015). Using rats aged around 4-6 months is the equivalent to 18-25 years of a human life span (Sengupta, 2012).

Treadmill Intervention

In order to reduce stress and potential stress-related experimental confounds, all animals were given a period of five days to acclimate to their new surroundings prior to any experimental manipulation. During the acclimation period, all animals were handled daily and allowed to explore the treadmill apparatus that was used in the experiment once a day for three days prior to experimentation. Day 1—10 min at 10m/min, Day 2—15 min at 12 m/min, Day 3—20 min at 15m/min (Burghardt, Fulk, Hand, & Wilsona, 2004). The LE8710RTS Five Lanes Touch Screen Treadmill (Panlab Harvard Apparatus) was used during this experiment. Panlab/Harvard Apparatus small animal treadmills are used for forced exercise training and provide accurate testing of fatigue in rodents.

Procedures

This study consisted of four groups. Group one was exercise/saline group; this group received saline injections and exercise on specified day. Group two was no exercise/saline group; this group received just saline injections. Group 3 was exercise/oxycodone; this group received injections of oxycodone and exercise as well, on specified day. Group four was no exercise/oxycodone; this group received just oxycodone injections. The week of experimentation, the first cohort of rats (groups one and two) were removed from their home cages and injected with saline for 13 days at the same time of day. Rats were then placed back in their home cages. Tolerance for opioids can be produced rapidly in rats, typically within 2 weeks (Wakim, 2012).

This study took place over 19 days per cohort. On day fourteen, group one walked on the treadmill for 1 hour at 15m/min. Withdrawal was assessed in both exercise and no

exercise groups by an injection of 1.0 mg/kg of naloxone on day 14 right after the treadmill exercise for group one. Group two was injected with 1.0mg/kg of naloxone after group one was complete. Withdrawal behaviors were then recorded. Naloxone is an opioid antagonist, which speeds up the process of withdrawal (Wheeler, Eliza, Jones, Stephen, Gilbert, Michael & Davidson, 2010).

When the second cohort of rats arrived, they were allowed the same time of handling and treadmill acclimation as cohort one. During the week of experimentation for the second cohort, each rat in groups three and four were given opioid injections for 13 days. Due to manufacturing and time constraints, 10mg/kg of morphine had to be administered to groups three and four for two days, while the shipment of oxycodone arrived. The third day of injections, 10 mg/kg of oxycodone was then administered for the rest of the injection time frame. Day fourteen for the second cohort, group three walked on the treadmill for the same time, (1 hour at 15m/min) and group four remained in their home cages (Alaei, Borjeian, Azizi, Orian, Pourshanazari, & Hanninen, 2006). Naloxone was then administered to group three and four at 1.0mg/kg right after the treadmill task for group three. Group four received the same naloxone injection after group three was complete. Withdrawal behaviors were then recorded.

Observer's blind to the study analyzed withdrawal behavior for 30 min by observing a video that was taken of the rats during this period; Inter-rater reliability was calculated from the scores obtained by the raters (Miladi-Gorji, Rashidy-Pour, & Fathollahi, 2012; Kaka, Rahmanzade, Safee, & Haghparast, 2014; Azizi, Ranjbar-Slamloo, & Semnanian, 2012; Liu, Rockhold, & Ho, 1999). Withdrawal signs were recorded and scored according to

a modified version of the Gellert–Holtzman scale (Miladi-Gorji, et al., 2012; Hammami-Abrand Abadi, Miladi-Gorji, 2016): wet dog shakes (lateral and rotary motions of the head), (Richardson, McLemore, & Gauda, 2006), (1-2 shakes = 2; 3 or 4 shakes = 3; 4 or more shakes = 4), escape attempts, (leaping off the surface with all four paws), (Xiaohui, Cao, Guo, & Zhao, 2006), (2-4 attempts = 1, 5 to 9 attempts = 2, and 10 or more attempts = 3), abnormal posture/writhing, (the rat lies on the floor, while the belly is firmly pressing the surface; abdominal contractions are usually present), (Xiaohui, et al., 2006), teeth chattering, (the rat rapidly clicks teeth together), (Xiaohui, et al., 2006), and profuse salivation was scored for their presence and latency to first occurrence.

A camera was set up in the lab to record withdrawal effects, allowing for the observers' blind to the study to analyze the behavior. Immediately following testing for withdrawal, all rats were returned to standard cages and given unrestricted access to food and water. After experimentation was complete for each cohort, all 20 rats were euthanized.

RESULTS

The total sample size was 38 rats from both cohorts. There were ten rats per group, with two rats, one from group three and one from group four dying in week one and week two respectively. There were four groups overall, including exercise saline, no exercise saline, exercise oxycodone and no exercise oxycodone (see Table 1).

Table 1

Group 1	Group 2	Group 3	Group 4
Exercise/Saline	No exercise/Saline	Exercise/Oxycodone	No exercise/Oxycodone

Note: Each group for the study and what the group consists of.

Interrater reliability was conducted with Cronbach's alpha estimate of internal consistency, for scores from each rater for each withdrawal behavior (see Table 2).

Table 2

	Profuse Salivation	Abnormal Posture	Teeth Chatter	Escape Attempts	Wet Dog Shakes
Cronbach's Alpha	.880	1.0	.935	.856	.573

Note: The interrater reliability for the withdrawal behaviors from both raters.

The results indicated the satisfactory level of internal consistency for the withdrawal behaviors between the raters. Due to teeth chatter, profuse salivation, and abnormal posture being on a latency time scale, and escape attempts and wet dog shakes being on a scoring scale, all variables were transformed into Z-scores to place everything on the same scale.

Z-scores from each withdrawal behavior were then combined in order to compute an overall withdrawal score for each animal. In order to test the hypothesis that exercise will potentially mediate withdrawal, a MANOVA was conducted between each withdrawal behavior to group. There was a significant difference for average teeth chatter between groups, $F(3, 34)= 85.782$, $p<.001$. Post hoc test using Bonferroni revealed statistical significance for teeth chatter between group (see Table 3) and (Figure 1).

Table 3

	Group	Group	Sig.
Teeth Chatter	1	3	.000***
	2	4	.000***
		3	.000***
		4	.000***
Abnormal Posture	1	3	.000***
	2	4	.000***
		3	.000***
		4	.000***
Wet Dog Shakes	1	3	.010***
	2	4	.001***
		3	.010***
		4	.001***

Note: The significant withdrawal behaviors between group of the MANOVA. 1 represents exercise/saline. 2 represents no exercise/saline. 3 represents exercise/oxycodone. 4 represents no exercise/oxycodone. *p<.05, **p<.01, ***p<.001

Figure 1

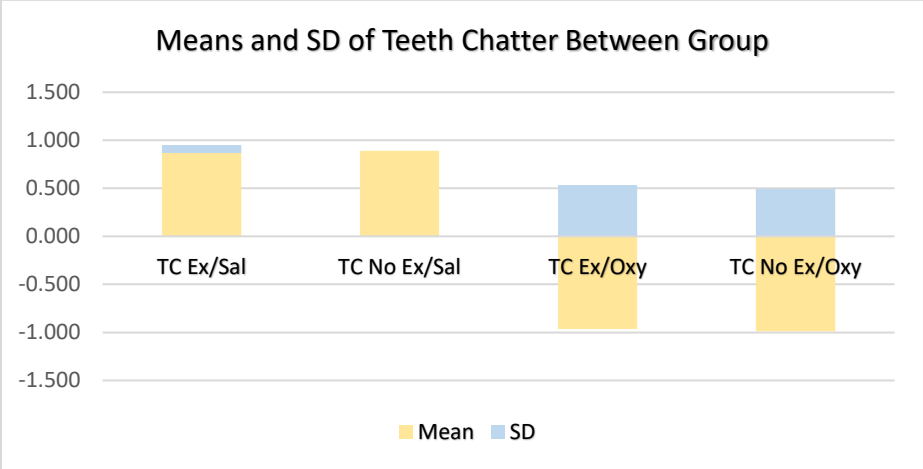

Figure 1. A chart showing the means and standard deviations of teeth chatter between each group.

There was a significant difference for abnormal posture between groups, $F(3, 34)= 101.162$, $p<.001$. Post hoc test using Bonferroni revealed statistical significance for abnormal posture between group (see Table 3) and (Figure 2). There was a significant difference for wet dog shakes, $F(3, 34)= 10.477$, $p<.001$ between groups.

Figure 2

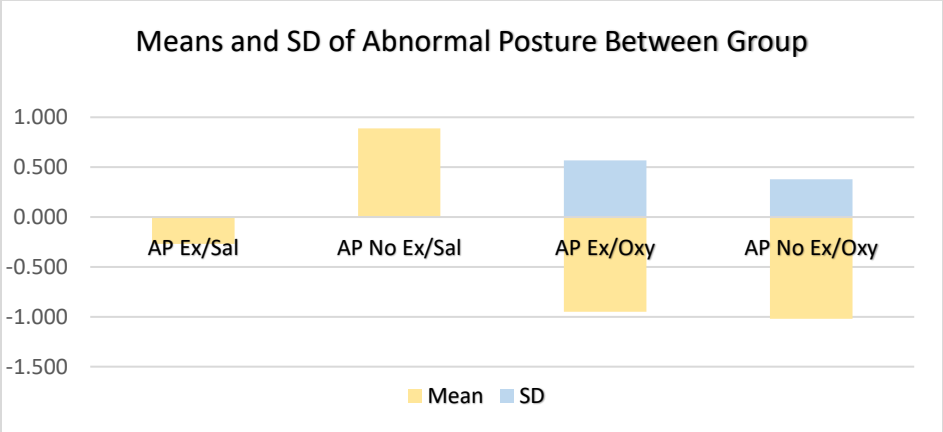

Figure 2. A chart showing means and standard deviations of abnormal posture between each group.

Post hoc test using Bonferroni revealed statistical significance for wet dog shakes between group (see Table 3) and (Figure 3).

Figure 3

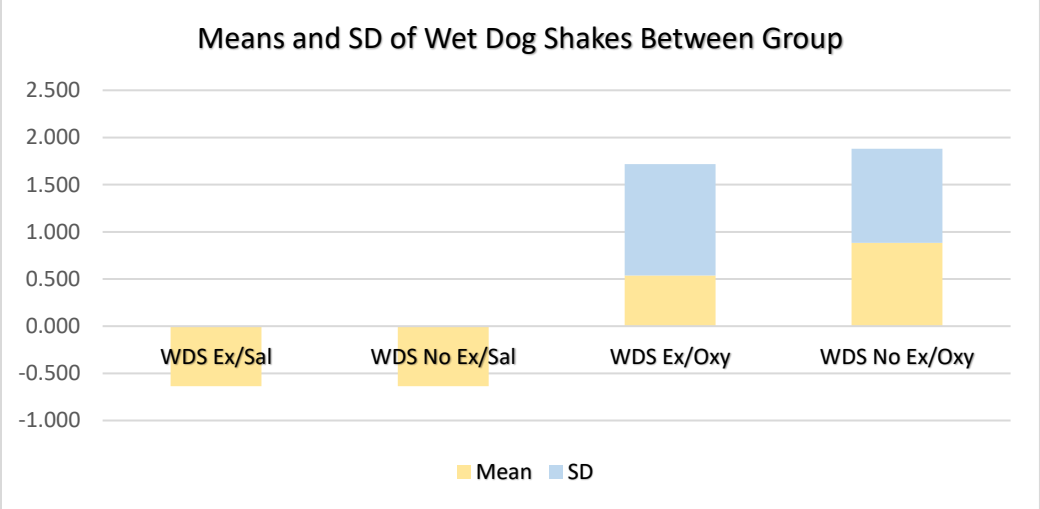

Figure 3. A chart showing the means and standard deviations of wet dog shakes between each group.

There was no significant difference for escape attempts (p>.05) between groups. Means and standard deviations for each significant withdrawal behavior between group can be seen in Table 4.

Table 4

	Group 1	Group 2	Group 3	Group 4
Teeth Chatter	M=.86 (SD=.08)	M=.89 (SD=.00)	M=-.96 (SD=.49)	M=-.98 (SD=.49)
Abnormal Posture	M=-.26 (SD=.00)	M=.88 (SD=.00)	M=-.95 (SD=.56)	M=-1.0 (SD=.37)
Wet Dog Shakes	M=-.63 (SD=.00)	M=-.63 (SD=.00)	M=.53 (SD=1.1)	M=.88 (SD=1.0)

Note: Means and standard deviations of the MANOVA for the significant withdrawal behaviors between group. Group 1 represents exercise/saline. Group 2 represents no exercise/saline. Group 3 represents exercise/oxycodone. Group 4 represents no exercise/oxycodone.

Two-way ANOVA was conducted to compare the two independent variables (i.e. exercise and drug), to overall withdrawal. There was no significance difference between exercise conditions and overall withdrawal, $F(1, 34)= .118$, $p= .733$. There was however a significant difference between saline and oxycodone when examining overall withdrawal, $F(1, 34)= 18.569$, $p<.001$. Comparing exercise and no exercise within the saline condition, there was no significant difference, $F(1, 34)= .001$, $p=.997$. There was no significant difference when comparing exercise and no exercise within the oxycodone condition, $F(1, 34)= .199$, $p=.658$. There was a significant difference when comparing saline and oxycodone between the exercise groups, $F(1, 34)= 10.639$, $p=.003$. There was also a significant difference when comparing saline and oxycodone between the no exercise groups, $F(1, 34)= 8.022$, $p=.008$. Means and standard deviations for each significant withdrawal behavior between group can be seen in Table 5.

Table 5

	M	*SD*
Group 1	.22	.01
Group 2	-.28	.55
Group 3	.22	.00
Group 4	-.21	.41

Note: Means and standard deviations for the Two-Way ANOVA between group.

DISCUSSION

The current study hypothesized that exercise would mediate withdrawals. The findings from the MANOVA showed significance for three of the withdrawal behaviors, which suggests that these specific behaviors have an impact on overall withdrawal. It is possible that certain withdrawal behaviors such as teeth chatter, abnormal posture and wet dog shakes, are more common behaviors seen in withdrawal and therefore had more data recorded. These behaviors might be more common because during drug withdrawal, the body will naturally give off these behaviors, while the drug is being detoxed from the body (Shah, Huecker, 2019). The Two-way ANOVA results show that exercise did not mediate withdrawals. However, there was a difference between saline and oxycodone, suggesting oxycodone impacted withdrawal which is to be expected.

Exercise has many benefits on the brain and body that activate pathways the same way a drug does. In the future, exercise could be further explored at different time points over an extensive period of time. Another point to note, the administration of oxycodone could be given at intervals of two times a day to ensure dependence on that drug. This research still shows that rats were able to become dependent on oxycodone because they experienced withdrawal. Even though the differences between saline and oxycodone conditions were minimal, some possible explanations could be sample size and duration of time that could have impacted the study.

Exercise will always be a crucial part in maintaining overall body and brain health (Trivedi, et al., 2007). More research needs to be done on this topic of opioids because of its growing concern.

There are many treatment methods mentioned previously that have shown to be effective for patients. If there is a way to use natural methods to aid patients in getting back to their homeostasis, that research should be expanded. Future research can always improve this method as well as show support for exercise potentially mediating opioid withdrawals.

Limitations

Limitations during this study were the sample size in each group. With an increase in sample size, there is always a possibility that it would provide more accurate mean values and greater power (Faber, Fonseca, 2014). The morphine administration for two days before oxycodone was used because the oxycodone had not come in yet. The administration of morphine was at the same dose and same volume calculation as was the oxycodone for the rest of the study. Morphine is very similar to oxycodone regarding the chemical properties of potency and affinity (Trivedi, et al., 2007). Even though they may have some percent differences, the choice to administer morphine first was the safer option to allow for the rats to ease into the transition of morphine to oxycodone (Trivedi, et al., 2007). Each limitation was addressed properly and with the high concern of the safety for the animals and research assistants in the lab.

Implications and Concluding Remarks

This study extended the literature on the opioid epidemic as well as the complications with patients struggling with opioid withdrawal (Mehendale, et al., 2013; Joranson, et al., 2000). There is extensive research regarding opioids and the major complications behind what they do (Mehendale, et al., 2013; Joranson, et al., 2000). The research is growing so that the public can understand how to treat or assess patients/people going through an opioid

abuse or addiction (National Institute on Drug Abuse, 2019). With the treatment centers doing what they can do to help ease the stress and irritability to their patients by providing medication, there is always more ways to address withdrawal (National Institute on Drug Abuse, 2019).

This study focused on exercise as an adjunctive method to opioid antagonists (Greenwood et al., 2011; MacRae et al., 1987). Other research has supported that exercise has been shown to mediate withdrawal (Greenwood et al., 2011; MacRae et al., 1987). The research from these articles involve different extended time, methods, opioids and support for why exercise is a possible alternative (Greenwood et al., 2011; MacRae et al., 1987). Other research has reported that exercise does mediate withdrawal behaviors in opioid dependent rats (Alaei, et al., 2006; Hosseini, et al., 2009; Mokhtari-Zaer, et al., 2014; De La Garza, et al., 2016). The methods and procedures these researchers used, consisted of different exercise time frames, different opioids, and multiple time points/injection dosages compared to this current study (Alaei, et al., 2006; Hosseini, et al., 2009; Mokhtari-Zaer, et al., 2014; De La Garza, et al., 2016). Research has shown support for the opioid crisis that is rising in our society today (Joranson, et al., 2000). Prescriptions and insurance can also add to the negative consequences to those trying to get better/well (Joranson, et al., 2000).

Research like the one conducted here, is trying to provide help and support for people in treatment facilities that have gone through extensive medication to get their heath back. Exercise has been shown is other literature to reduce the severity of withdrawal (Mokhtari-Zaer, et al.,, 2014; Alaei, et al., 2006). The hope and goal from this study is to potentially educate researchers passionate about treatment, withdrawal, addiction, exercise and drug

compounds, that there is always an alternative. Other methods are constantly on the rise and maybe future precautions can be taken to put patients first and help find a successful treatment for exercise and opioid withdrawals.

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APPENDIX A

ANGELO STATE UNIVERSITY
College of Graduate Studies & Research
Institutional Animal Care & Use Committee

February 18, 2020

Dr. Steven Brewer, Assistant Professor
Department of Psychology and Sociology
Angelo State University
San Angelo, TX 76909

Your proposed project titled, "Influence of Exercise on Oxycodone Withdrawal in Rats" Amendment was reviewed by Angelo State University's Institutional Animal Care and Use Committee (IACUC) in accordance with the regulations set forth in the Animal Welfare Act and P.L. 99-158.

This protocol was approved for three years, effective February 18, 2020 and it expires three years from this date; however, an annual review and progress report form (www.angelo.edu/content/files/22583-iacuc-annual-review-progressreport) for this project is due on August 15 of each year. If the study will continue beyond three years, you must submit a request for continuation before the current protocol expires.

The protocol number for your approved project is 2019-108. Please include this number in the subject line of in all future communications with the IACUC regarding the protocol.

Sincerely,

Chase Runyan, Ph.D.
Co-Chair, Institutional Animal Care and Use Committee

BIOGRAPHY

Lacey Colleen Voth is a Masters' student at Angelo State University. She studied Behavioral Neuroscience in the Experimental Psychology program. Lacey earned her bachelor's degree in Psychology at Angelo State University as an undergraduate. Lacey has worked with animal and human research for five years. Lacey spent her second year as a graduate student taking classes and working on her thesis. Over the past four years, Lacey has presented at seven conferences with her research. Her admiration for neuroscience continues to grow in all aspects of her research. Lacey plans to pursue a career in surgical sales after obtaining her master's degree. No matter where life takes Lacey, she will always remember the love she has for neuroscience and the significant amount of growth she has gone through to be the person she is today.