Aerobic Exercise: An Adjunctive Therapy for Buprenorphine/Naloxone Retention in Opioid Use Disorder

Timothy Fong
Yale Physician Associate Program, timothy.fong@yale.edu

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Aerobic Exercise: An Adjunctive Therapy for Buprenorphine/Naloxone Retention in Opioid Use Disorder

A Thesis Presented to
The Faculty of the School of Medicine
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In Candidacy for the degree of
Master of Medical Science

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Timothy Fong, PA-SII
Class of 2020
Yale Physician Associate Program

Dr. David Fiellin
Professor of Medicine
YSM, Department of Internal Medicine
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Abstract

Opioid agonist treatment has been shown to reduce mortality, comorbid infections, and opioid cravings in patients with opioid use disorder. However, patient long-term retention on opioid agonist treatment is low and hindered by neurobiological and physiological changes caused by chronic opioid use, such as increased baseline noradrenaline and hyperalgesia. Some of these changes have been shown to be reversible or preventable with aerobic exercise. In this randomized clinical trial, we will determine whether an outpatient, adjunctive, aerobic exercise program designed around personal preferences can improve the retention on opioid agonist treatment. We will randomize 270 study subjects initiated on buprenorphine treatment to the exercise program and measure treatment retention at 1 year. This study will evaluate a patient-centric intervention that may increase quality of life for individuals with opioid use disorder.
Chapter 1: Introduction

1.1 Background: Opioid use disorder: Epidemiology, diagnosis, and treatment
From 1999 to 2017, annual deaths caused by opioid overdose has risen from 8,050 to 47,600.1 This substantial increase in deaths cements opioid overdose as the leading cause of unintentional deaths in the United States, leading the US Department of Health and Human Services to declare the opioid crisis a public health emergency in October 2017.2 Concern for opioid misuse extends beyond mortality, as of 2018, approximately 2 million people in the United States carry the diagnosis of opioid use disorder (OUD) and experience the sequelae associated with it.3 Like other misused substances, opioids can cause continuous craving and use that may often hinder one’s mental, social, and physical wellbeing. Additionally, those who use opioid intravenously can be exposed to skin infections that can become systemic if untreated, as well as significant blood borne infections including HIV, hepatitis B, and hepatitis C.4

Financially, OUD costed the United States health system over $78 billion in treatment in 2013, more than other prominent chronic diseases such as asthma, stroke, and HIV infections.4

OUD was defined by the fifth edition of Diagnostics and Statistics Manual of Mental Disorders (DSM-5) in 2013 as recurrent opioid use leading to fulfillment of at least two of eleven criteria. These criteria range from craving of use to disruption of one’s social, occupational, and recreational activities. A thorough substance use questionnaire and history is critical in elucidating if one meets these criteria. Physical exam findings are often minimal in people who are not actively intoxicated or withdrawing apart from track marks in those who misuse intravenously.

With OUD’s prevalence in the United States at an all-time peak, it may seem paradoxical that there have been effective and safe medications available for over three decades. Methadone and buprenorphine are the two main medications available, with methadone being an opioid
agonist and buprenorphine a partial opioid agonist. As opioids, they both lead to cross-tolerance
to other opioids and bind to mu receptors with high affinity, but with lower intrinsic activity such
as euphoria and sedation while beneficially decreasing opioid craving and withdrawal symptoms.
Their high mu receptor affinity blocks binding and subsequent activation of the receptor from
exogenous opioids. Clinical trials have shown both medications to be efficacious in increasing
social functioning, reducing illicit opioid use, decreasing mortality, as well as reducing risk of
infections through intravenous drug use.\textsuperscript{5-7} Regulations have greatly expanded access to opioid
agonist therapy across the United States in the past two decades.\textsuperscript{8, 9} DATA 2000 allowed
buprenorphine to be prescribed in the clinic by physicians who have completed an 8-hour
training course.\textsuperscript{10} Revision of the Comprehensive Addiction and Recovery Act in 2016 extended
buprenorphine prescribing privileges to nurse practitioners and physician assistants who
complete a similar 24 hours of training.\textsuperscript{11} Regulation in administration and prescription of both
medications is due to their potential for misuse. Methadone can only be dispensed by certified
opioid treatment programs and is a schedule II medication. Buprenorphine combined with
naloxone has the added benefit of naloxone’s opioid antagonist properties when misused
intravenously, discouraging misuse by precipitating withdrawal symptoms. Buprenorphine is
classified as a schedule III medications due in part to this benefit, allowing it to be prescribed by
experienced and trained providers and dispensed by pharmacies.\textsuperscript{12}

1.2 Statement of the Problem

The current standard of care with opioid agonist treatment is ongoing (“maintenance”)
therapy; it has been shown to be superior to medically supervised withdrawal (“detoxification”)
in terms of preventing relapse.\textsuperscript{13} However, a 2018 survey showed that only about 59% of patients
with OUD receive medication.\textsuperscript{3} A more glaring issue is that of that 59% who receive treatment,
only a fraction of those individuals remained in treatment. Individual clinical trials and cohort studies have shown buprenorphine adherence rate in the United States ranges from 40 – 60% at 12 months with the range likely due to different definitions of adherence, different eligibility criteria, or induction speed of buprenorphine. Even on the high end of the retention range, this equates to only 35% of patients with OUD receiving and adhering to their medication nationally. The cause of this low percentage is multifactorial with some factors being more remediable than others. Disrupted sleep, hyperalgesia, psychological stress, other substance use, and mental health disorders are just some of the prominent factors associated with OUD and good predictors of poor treatment retention. Controlling or correcting these factors through the use of an adjunctive therapy could theoretically augment the retention rate of buprenorphine.

Presently, there is no known adjunctive therapy with strong evidence to support its role in increasing retention to opioid agonist therapy. With roughly 38% of patients seeking treatment for OUD having a diagnosed psychiatric disorder, behavioral therapy is a logical adjunctive therapy and often recommended with opioid agonist treatment in efforts to increase treatment retention. However, recent systematic reviews showed adjunctive behavioral therapy does not lead to a statistically significant increase in treatment retention compared to opioid agonist therapy alone.

The proposed randomized controlled trial will aim to solve this gap in current treatment of OUD with the use of an adjunctive aerobic exercise intervention. Aerobic exercise has a well-established efficacy in many chronic diseases such as fibromyalgia and hypertension. Increasing evidence from observational studies to preliminary randomized controlled trials have pointed to its efficacy in substance use disorders such as marijuana, alcohol, and nicotine as well. However, only a single pilot study to date has explored the utility of aerobic exercise in
the OUD population. Clinical trials have shown aerobic exercise’s positive effect on disrupted sleep, hyperalgesia, psychological stress, other substance use, and mental health disorders, the same factors associated with poor buprenorphine treatment retention. Given these observations, the potential for aerobic exercise to increase buprenorphine treatment retention rates in the OUD population is certainly plausible and a possible relationship that should be explored further.

1.3 Goals and Objectives
The goal of this randomized controlled trial is to determine if a structured aerobic exercise intervention would significantly raise buprenorphine retention at 1 year in patients with OUD who are initiating treatment.

1.4 Hypothesis
Patients with OUD initiated on buprenorphine who receive an aerobic exercise intervention, designed around their preferences for three one-hour sessions a week will have a higher rate of buprenorphine treatment retention compared to those receiving a time and attention control of sedentary activities over 1 year.

Secondary hypotheses are that patients receiving the intervention will have lower amounts of illicit drug and opioid use, number of opioid overdoses, number of missed buprenorphine doses, and an increase in quality of life measured by the Medical Outcomes Study Short-Form 36 Health Survey over 1 year.

Hypothesis 1 (primary):
Null hypothesis: There is no association between aerobic exercise and buprenorphine treatment retention in patients with OUD.
Alternative hypothesis: There is a positive association between aerobic exercise and buprenorphine treatment retention in patients with OUD.

**Hypothesis 2 (secondary):**
Null hypothesis: There is no association between aerobic exercise and number of opioid overdoses in patients with OUD.

Alternative hypothesis: There is a positive association between aerobic exercise and number of opioid overdoses in patients with OUD.

**Hypothesis 3 (secondary):**
Null hypothesis: There is no association between aerobic exercise and illicit drug use in patients with OUD.

Alternative hypothesis: There is a positive association between aerobic exercise and illicit drug use in patients with OUD.

**Hypothesis 4 (secondary):**
Null hypothesis: There is no association between aerobic exercise and missed buprenorphine doses in patients with OUD.

Alternative hypothesis: There is a positive association between aerobic exercise and missed buprenorphine doses in patients with OUD.

**Hypothesis 5 (secondary):**
Null hypothesis: There is no association between aerobic exercise and quality of life in patients suffering from OUD.

Alternative hypothesis: There is a positive association between aerobic exercise and quality of life in patients with OUD.

**1.5 Definitions:**
**Opioid use disorder (OUD)** is defined by DSM-5 as anyone having at least 2 of the following 11 criteria in the past 12 months:
1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Exhibits tolerance where tolerance is defined as either a need for markedly increased amounts of opioids to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount of an opioid.
11. Exhibits withdrawal where withdrawal is defined as either the characteristic opioid withdrawal syndrome or the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.

Severity of OUD is based on the number of criteria above met and categorized as mild (2-3), moderate (4-5), and severe (6+).
**Aerobic Exercise** is defined by the American College of Sports Medicine as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature. Current recommendations for the healthy adult consist of 150 minutes of moderate intensity exercise per week. We will refer to aerobic exercise as moderate and vigorous intensity aerobic exercise, defined by the American College of Sports Medicine as ≥40% heart rate reserve, in the methodology.

**References**

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Chapter 2: Review of Literature

2.1 Introduction

A literature search through the PubMed, Scopus, and OVID Medline databases was conducted between July 2019 and April 2020, searching for articles related to aerobic exercise and buprenorphine adherence. Keywords used in the search either in combination or independently included aerobic exercise, exercise, physical activity, buprenorphine, methadone, opioid agonist therapy/treatment, opioid-related disorder, substance use, compliance, adherence, and treatment outcomes. Articles with abstracts pertinent to our study were identified and reviewed.

2.2 Review of Relevant Literature

A. Opioid Use Disorder Etiology

OUD is a chronic disease that commonly develops from abuse of prescription opioids or initial use of illicit opioids for their euphoric effect. The majority of the OUD population originates from prescription opioid misuse and illicit heroin misuse.¹ A 2018 report showed that of the 9.9 million Americans who misused prescription opioids, 57.8% of them obtained the medication through means other than a doctor.² A 2015 systematic review estimated that 6-8% of the millions of Americans prescribed opioids end up being diagnosed with OUD.³ Many of these individuals turn to illicit opioids such as heroin and fentanyl as a cheaper alternative to cope with OUD. The exact reason why certain individuals end up with OUD while others do not is still unclear. However, multiple studies have associated OUD with comorbid mental disorders, current or past use of other illicit substances, and a family history of substance misuse.⁴

Contrary to popular belief, OUD is not simply a choice made by patients, but rather an intricate modification of chemical signals in the brain with multiple mechanisms that lead to addiction among those who are exposed to illicit or prescribed opioids.⁵ Opioids bind to 3
different central nervous system transmembrane neurotransmitter receptors: mu, kappa, and delta. In OUD, the binding and activation of the mu receptor sets off a biochemical cascade that affect various parts of the brain, one of them being the mesolimbic reward system. Neurons activated in the ventral trigeminal area (VTA) releases dopamine to the nucleus accumbens (sense of pleasure) and the hippocampus (retains memory of pleasure). Chronic opioid use reduces the amount of dopamine release to the nucleus accumbens. This leads to what is colloquially called tolerance, a greater amount of opioids is needed to reproduce the same euphoric effects. Additionally, the amount of pleasure obtained from normally euphoric activities is reduced such that one is dependent on opioids to experience euphoria. The pleasurable memories implanted in the hippocampus cause the sense of craving, further propelling one towards repeated opioid use through activation of VTA glutamate neurotransmitters which activate the aforementioned dopamine neurons.

Another obstacle in treating addiction is the uncomfortable withdrawal symptoms including diarrhea, myalgia, and anxiety that often lead to relapse. Opioids binding to mu receptors in the locus coeruleus (LC) suppress the LC’s ability to produce noradrenaline. However, LC neurons are able to adjust to the chronic suppressive effects of continuous opioid use and increase their baseline level of noradrenaline production to counteract the suppressive effect of opioids. In the event of opioid abstinence, the suppression of noradrenaline is absent and the excess amount of noradrenaline produces the classic opioid withdrawal symptoms. VTA glutamate neurotransmitters also have a role in the activation of LC neurons; opioid abstinence excites the neurotransmitters, stimulating noradrenaline release from LC neurons and further enhancing withdrawal symptoms.\(^5\)
B. Potential Mechanism of Action of Aerobic Exercise

Relapse is often cited as one of the primary non-logistical reasons for patients that prematurely discontinue buprenorphine treatment.\textsuperscript{6} Although buprenorphine is highly effective at ameliorating craving and withdrawal symptoms,\textsuperscript{7} it does not address other symptoms that the OUD population faces to remain abstinent.

Opioid induced hyperalgesia is a phenomenon arising from chronic opioid use where the user is more sensitive to painful stimuli.\textsuperscript{8} Hyperalgesia has been observed in buprenorphine users in multiple studies. Athanosos et al. (2018)\textsuperscript{9} observed the pain tolerance of twelve individuals receiving buprenorphine compared to a control group consisting of ten participants. Pain tolerance was measured with the cold pressor response where participants immersed their nondominant arm in 0.5ºC–1.5ºC water, it was quantified as the number of seconds the participants took to remove their arm from the water. Individuals receiving buprenorphine were found to have significantly lower pain tolerance levels compared to the control group (ANOVA $P = 0.009$, 95% CI $= -5$ to $-30$). Athanosos et al. further explored if pain tolerance in buprenorphine users would improve with an infusion of morphine. While the control group’s pain tolerance increased significantly with the morphine infusion ($P < 0.05$, 95% CI $= 2$ to 34), there was no statistically significant differences in pain tolerance with individuals receiving buprenorphine after morphine infusion ($P > 0.45$), suggesting that an alternative therapy for analgesic control is needed in this population. Although this study is limited by its small sample size, similar findings were observed by Wachholtz and Gonzalez (2014)\textsuperscript{10} in their 120-subject study. The pair similarly used the cold pressor response, but quantified pain tolerance as sensitivity to pain (time to first experiencing pain) as well as tolerance (time to removing an arm from the water). The study participants were separated equally into four different groups:
individuals receiving methadone; individuals receiving buprenorphine; those with a history of opioid agonist therapy; opioid naïve control. Present and past users of opioid agonist therapy had no significant differences in sensitivity and tolerance between one another, but all had significantly increased sensitivity and decreased tolerance (28.2 and 61.4 seconds respectively) compared to the control group (54.4 and 137.1 seconds respectively; p<0.001). Both studies captured this correlation at a single point in time; it remains unclear if buprenorphine therapy is associated with sustained decreased pain tolerance. However, both studies still demonstrated an acute correlation between buprenorphine therapy and decreased pain tolerance; an adjunctive therapy that could increase pain tolerance in a safe and efficacious manner would benefit this population.

Aerobic exercise is largely safe and potentially efficacious in inducing hypoalgesia with several reviews supporting its hypoalgesia effects.¹¹,¹² Naugle et al.’s (2012)¹¹ meta-analytic review consisted of eight studies that involved aerobic exercise and a measurement of pain tolerance. These studies measured pain tolerance in various ways including pressure, heat, and cold stimuli; all studies measured pain tolerance before and after a single aerobic exercise session ranging from ten to thirty minutes. The effect size for pain threshold was positive and moderate (0.48 and 0.43 when adjusted for sample size and bias). All these studies notably measured an acute rise in pain threshold shortly after exercise and did not assess pain threshold longitudinally. Comparatively, studies observing effect of chronic aerobic exercise on pain tolerance and sensitivity is rather limited. Jones et al. (2014)¹³ aimed to address this gap with their six-week study. Half of the 24 participants enrolled in 18 sessions of cycling for 30 minutes each session at 75% of HR reserve. The primary outcomes of the study were ischemic pain tolerance and pressure pain thresholds. At the end the study, the aerobic exercise group had a
significant increase in ischemic pain tolerance ($t_{11} = -3.15$, $P = 0.036$, +20.3%), while the control group was unchanged. However, there was no significant effect on pressure pain threshold in either the upper or lower body. ($F_{1,22} = 0.6$, $P = 0.45$ and $F_{1,22} = 2.9$, $P = 0.1$ respectively). Other than the low sample size, this study had other notable limitations. Participants were not randomized and the study lacked a time and attention control, this led to the intervention group receiving more attention than the control group. Nonetheless, the study showed promising effects for sustained pain tolerance with chronic aerobic exercise.

Sleep disturbances are another challenge that the OUD population encounters. A 2017 cross-sectional study\textsuperscript{14} surveyed 185 patients enrolled in opioid agonist therapy on their sleeping habits using the Medical Outcomes Study Sleep Scale.\textsuperscript{15} Patients commonly reported not getting the amount of sleep they needed (42.9%), not getting enough sleep to feel rested (39.6%), problems falling asleep (23.3%) and falling back to sleep after awaking (25.8%). Overall, 51.3% of the study’s patients were classified as having impaired sleep with no significant difference between buprenorphine and methadone therapy. Sleep quality is poorer in nonadherent patients; a retrospective study by Krishnamurthy et al. (2019)\textsuperscript{16} observed that poor sleep quality is highly prevalent among those who dropped out of buprenorphine treatment within six months. Sleep quality was assessed on 70 patients using the Pittsburgh Sleep Quality Index (PSQI)\textsuperscript{17} with a score <5 indicating poor sleep quality; 63% of males and 80% of females scored <5. Both these studies are limited as they used self-reported modalities to assess for sleeping disturbances. Both sampled patients from an isolated region (Baltimore and central Pennsylvania respectively) which limits the external validity of these findings. Limitations aside, these observations suggest poor sleep quality is highly prevalent in buprenorphine users and a poor predictor of treatment retention.
Although there is currently no known mechanism on how aerobic exercise improves sleep quality exists, growing evidence suggests a strong association between the two. A 2012 systematic review\textsuperscript{18} of six randomized clinical trials showed significant improvements in sleep quality measured by the PSQI (standard mean difference (SMD) of 0.47, 95\% CI 0.08 to 0.86) with exercise. Sleep latency was notably reduced as well (SMD 0.58, 95\% CI 0.08 to 1.08). Five of the six trials consisted of aerobic exercise, requiring participants to reach 60\% of their heart rate reserve; duration of the trials ranged from 10 to 16 weeks. The study utilized the PEDro scale, a grading system assessing for areas of bias. The studies included had PEDro scale ranging from five to eight, indicating high internal validity.\textsuperscript{19} This strict study inclusion criteria limited Yang et al. to a smaller (305 participants), predominantly female sample (79\%). Notably all the studies sampled adults over 40 years old.

C. Factors Associated with Buprenorphine Nonadherence

Opioid agonist therapy has been repeatedly proven to be effective in OUD outcomes, reducing mortality, relapse, intravenous related infections, and quality of life among others.\textsuperscript{20} Its effectiveness is predicated on treatment adherence; patients nonadherent to buprenorphine, defined as taking it less than 80\% of required times, are 10 times more likely to relapse to opioid misuse compared to adherent patients.\textsuperscript{21} Various studies have explored the predictive factors associated with buprenorphine nonadherence and found that many of these rectifiable factors are the same predictive factors for OUD (comorbid mental disorders, use of other illicit substances, psychosocial stability, etc.). An intervention attenuating these factors can theoretically lead to a desired increase in buprenorphine retention.
C1. Comorbid Mental Disorders

Recent studies examining the prevalence of comorbid psychiatric disorders in the OUD population found it to be an estimated 38%. Litz and Leslie (2017)\textsuperscript{22} further examined the specific psychiatric disorders within the buprenorphine population and found anxiety (22%) and major depressive disorder/bipolar (15.9%) to be the most common psychiatric comorbidities among this subset. Although anxiety was found to be the most common psychiatric comorbidity in this 2947 subject sample, it was not associated with lower adherence nonadherence (defined as medication possession ratio $\geq 0.8$) rates (odds ratio $0.975$, CI $0.810 - 1.173$, $p = .788$). However, with a $p$-value greater than 0.05 and a CI crossing 1, this was not statistically significant. Major depressive disorder/bipolar was found to be associated with lower adherence rates (OR $0.804$, CI $0.651 - 0.994$, $p = .044$), supporting previous literature findings of lowered medication adherence with a diagnosis of major depressive disorder/bipolar.\textsuperscript{23} The generalizability of this data to the whole population of those receiving buprenorphine is limited as this retrospective cohort study used the database, MarketScan, containing data only from private insurance. However, similar findings were observed in other studies focusing on associations of psychiatric disorders and buprenorphine.

Tkacz et al. (2011)\textsuperscript{21} found a similar percentage to Litz and Leslie; 24% of their 2,197 subject sample had a psychiatric issue. Patients nonadherent to buprenorphine had a higher psychiatric composite score compared to adherent patients ($0.285$ vs. $0.228$, $p = .036$). Adherence was also defined as medication possession ratio $\geq 0.8$. Psychiatric issues were notably assessed through the Addiction Severity Index, a self-reported assessment, and thus, prone to reporting bias.\textsuperscript{24} The demographics of this prospective cross-sectional study was more representative of the demographics of the OUD population.\textsuperscript{25} Although the demographics were
similar to the OUD population, this study population sought primary care, office-based buprenorphine treatment, which according to a 2010 report, comprised an estimated 46% of the buprenorphine treatment population from 2002-2009. Ambiguous directionality of an association is a common limitation in cross-sectional studies; however, the directionality of this study is clear. Subjects were seeking buprenorphine treatment at the time, affirming that psychiatric disorders lead to buprenorphine treatment.

The association between aerobic exercise and major depressive disorder relief is well documented in literature with numerous meta-analytic studies supporting a positive association between the two variables. Morres et al.’s 2018 meta-analysis of 11 studies examined this association in adults and found a significant antidepressant effect with aerobic exercise ($g = -0.79$, 95% CI $-1.01$, $-0.57$, $P < 0.00$) compared to non-exercise interventions. This meta-analysis differed from previous meta-analysis with its stringent eligibility criteria. Included studies recruited solely from mental health services as opposed to media advertisements which often attract patients with higher outcome expectations. This study utilized the PEDro scale and found most of the included studies had a PEDro scale $\geq 6$, indicating high internal validity. Though most of the included studies had a high PEDro score, all of them lacked a time and attention control. Supervised aerobic intervention was compared to various interventions such as pharmacotherapy and psychotherapy, none of the studies accounted for the potential confounding effect that staff interaction time would have on depression.
C2. Comorbid Drug Use

Similar to psychiatric disorders, substance use other than opioids is prevalent among the OUD population. Cocaine, alcohol, marijuana, and benzodiazepine use have all been linked to lowered buprenorphine treatment retention with cocaine being the most studied of the group.

Observational studies have found the prevalence of cocaine in people entering buprenorphine treatment to be an estimated 37-48.8%.$^{28, 29}$ Multiple cohort studies have observed the negative association between baseline cocaine use and buprenorphine treatment retention. In a secondary analysis of a randomized clinical trial examining psychosocial counseling and buprenorphine retention, Sullivan et al. (2010)$^{28}$ observed that baseline cocaine use in their 162 study population led to shorter treatment retention times (mean of 15.8 vs. 18.4 weeks, $p = .04$) and lower completion rates of their 24 week treatment (33% vs. 50%, $p = .04$). More concerning of an observation was that of the 63% baseline negative cocaine group, 31% of that group were found to have cocaine metabolites in urine drug samples taken during the study. The treatment retention in the subgroup of negative baseline cocaine use, but positive cocaine use during the study, was also lower compared to those who were cocaine abstinent throughout (mean of 19.0 vs. 16.5 weeks, $p = .003$).

In another secondary analysis of a randomized clinical trial comparing intensive outpatient buprenorphine to standard outpatient treatment, Gryczynski et al. (2013)$^{30}$ observed in their 297 study population that people entering the study with baseline cocaine use (measured with a urine drug sample) left treatment earlier (HR=1.71; 95% CI=1.18–2.48; $p=.004$) and had lower completion rates of their 6 month treatment (OR=2.05; 95% CI=1.25–3.35; $p=.004$). This study’s population consisted entirely of African Americans with a 61.9% male predominance,
contrasting well with Sullivan et al.’s 2010 study with a 76% Caucasian and 83% male population.

Although literature primarily indicates cocaine use’s negative association with buprenorphine treatment retention, Cunningham et al. (2014)\textsuperscript{31} observed no statistical significance in their 87 subject prospective cohort study between cocaine use and 6 month buprenorphine treatment retention (AOR=1.56, 95%CI=0.58–4.17, p=0.38) when adjusting for age, baseline opioid analgesic use, and history of incarceration. Participants in the study were predominantly male (73.6%) and Hispanic (73.2%) initiated on buprenorphine in a community health care clinic, limiting the generalizability of their study. Unlike other studies observing the association between cocaine use and buprenorphine, cocaine use was not objectively measured through a urine drug sample. Cunningham et al. measured cocaine use through self-report, leaving the study susceptible to reporting bias. As evident by Sullivan et al.\textsuperscript{28}, baseline negative cocaine users in buprenorphine treatment may initiate cocaine use during treatment leading to decreased buprenorphine retention rates. Cunningham et al. did not account for this occurrence, only measuring cocaine use at baseline, effectively assuming baseline negative cocaine users remained cocaine abstinence during the study.

Although there are no current FDA approved medications for treatment of cocaine use, a 2012 systematic review of 19 studies concluded that contingency management with cognitive behavioral therapy is effective at inducing cocaine abstinence.\textsuperscript{32} Though its efficacy is well supported, contingency management with cognitive behavioral therapy may not be ideal, especially in the context of concurrent buprenorphine use. Detractors of contingency management argue that this intervention does not alter internal motivations to change such that when a financial reward is withheld, patients will revert to baseline drug use. Aerobic exercise is
a potential treatment modality for cocaine use; multiple pre-clinical studies have observed reductions in cocaine use with aerobic exercise.\textsuperscript{33,34} To date, only one randomized clinical trial has been done exploring this observation. De La Garza et al. (2016)\textsuperscript{35} randomized 24 patients to three different study conditions, running, walking, and sitting for 30 minutes, 3 times a week, for 4 weeks. Both running and walking interventions were performed on a treadmill; the sole difference in these two study groups was the running group’s target heart rate was 75% of their maximum heart rate compared to 25% in the walking group. The sitting group served as the control condition and sat passively without access to sedentary leisure items throughout the 30 minutes. De La Garza et al. observed a statistically nonsignificant reduction in cocaine use measured by daily urine benzoylecgonine screenings ($F_{2,21}=1.7, p=0.21$). The failure to reject the null hypothesis may be due to the study’s low power (small sample size) and short study duration. Data was analyzed through the intention to treat analysis and any missing urine screenings were presumed to be positive, possibly contributing to a false reduction rate. Unlike most studies using exercise interventions, this study achieved a high (>90%) retention rate likely due to the use of contingency management; the completion of all 12 study sessions yielded participants $700. This study also interestingly observed that the walking and running groups produced similar reductions in cocaine use, raising the question of the intensity of aerobic exercise needed to reduce cocaine use.

D. Association Between Aerobic Exercise and OUD

Currently, the only randomized controlled trial examining the utility of exercise as an adjunctive treatment to opioid agonist treatment (methadone) was done by Cutter et al. in 2014.\textsuperscript{36} The study’s intervention of exercise was based on exergames on Wii Fit Plus while using a novel time-and-attention control of sedentary Wii games. Each patient self-reported illicit opioid and
cocaine use and completed questionnaires measuring psychological wellbeing before and after the 8-week study. Participants in both study conditions had a decrease in illicit drug use ($p < .001$, from $M = 3.0$ days/week to $M = 1.7$ days/week, $d = .82$), perceived stress ($p = .04$, $d = .50$), and an increase in optimism ($p = .04$, $d = .50$) after the study. Adherence rate was not statistically different between the two study conditions ($p = .34$, $d = .36$). However, the study had several features of note including a low exercise adherence of 62.7% in the intervention group, a low study size of 29 participants, and a short study duration of 8 weeks – less than the American College of Sports Medicine (ACSM) recommended 10 weeks minimum for research trials. The intervention in this study was also not a true aerobic exercise regime, patients completed 5 (2 aerobic, 1 strength, 1 balance, and 1 yoga) exergames in an average total of 20 minutes a day, 5 days/week. The researchers acknowledged that the exercise intervention was lacking in time compared to the American College of Sports Medicine minimum recommended amount of 2.5 hours/week. Though the validity of the study’s outcomes is limited due to the aforementioned limitations, there are numerous takeaways to draw from. The study’s primary outcome to see if exergames were an acceptable (defined as perception of enjoyment, usefulness, and achievement) and feasible exercise intervention. Patients in the intervention group rated the acceptability of the intervention a 6.3 out of 7 (SD 0.9) while the control group rated the acceptability of their time and attention control a 6.2 out of 7 (SD 0.5). The acceptable and novel time and attention control should be noted for future studies, previous studies utilizing exercise as an intervention fail to account for the time and attention required of exercise. Though adherence rate to the intervention and time and attention control were similarly low at 62.7% and 67.7% respectively, the study’s attrition rate of 7% shows exergames are a promising exercise intervention.
E. Review of Relevant Methodology

E1. Selection Criteria

Inclusion and exclusion criteria are relatively homogenous across exercise randomized controlled trials in the context of substance misuse. The components of an exclusion criteria aid to ensure participant safety, increase intervention adherence rates, and meet a study’s primary end point; they typically include medical conditions that interfere with aerobic exercise. Individuals currently treated with opioid agonist therapy have a higher pretrial probability of being retained in treatment as they have already shown a propensity of being successfully maintained for a select amount of time and should be excluded to avoid selection bias.

E2. Intervention

The prospect of aerobic exercise as a successful adjunctive treatment to buprenorphine is promising, but its efficacy may ultimately depend on the patient. Randomized clinical trials involving exercise as an intervention in the context of substance use are often plagued by low exercise adherence rates evident by the studies previously discussed, likely contributing to an underestimation of its benefits. Abrantes et al.’s 2011 study suggest individuals undergoing treatment for substance misuse are interested in engaging in an exercise program, though 47.4% of this study’s population consisted of patients undergoing treatment for alcohol misuse. Although patients desire to exercise, they may not enjoy rigid exercise protocols. A strong correlation between enjoyment of exercise and amount of exercise performed indicates that future studies should cater to the exercise preferences of patients in order to have a high adherence rate.
E3. Exercise Intensity

There is a positive association between exercise intensity and health benefits\textsuperscript{41} as well as exercise intensity and hypoalgesia\textsuperscript{11}, however, patients in Abrantes et al.’s\textsuperscript{39} study overwhelmingly preferred a moderate intensity. Additionally, higher intensity exercise has been linked to lower exercise adherence rates,\textsuperscript{42} though there is dispute in the literature.\textsuperscript{43}

E.4 Exercise Duration

The American College of Sports Medicine recommends a minimum of 150 minutes of moderate intensity exercise per week for healthy adults. Considering that most American adults fail to meet this criterion\textsuperscript{44}, it would be unreasonable to expect someone with OUD, likely to be even more sedentary at baseline\textsuperscript{39}, to do so. Beneficial results of exercise can still be observed in exercise sessions greater than 10 minutes\textsuperscript{43}, especially in previously sedentary individuals. Study protocols would ideally aim to gradually increase exercise duration; however, researchers also need to be sensitive to the patient’s increasing time commitment.

E.5 Additional Considerations

Catering to patient preferences may not be enough to overcome low exercise adherence rates. As previously mentioned, Cutter et al.’s\textsuperscript{36} exergame intervention was highly accepted by patients, yet intervention adherence rates remained low. While patients may relatively enjoy exercising, their lack of motivation can pose a barrier to higher adherence rates. In the previously mentioned 2016 De La Garza et al.\textsuperscript{41} study, the reported exercise adherence rate was 90\%, though the study was notably a third of the length of Cutter et al.’s\textsuperscript{36} study. Their use of
contingency management may have contributed to this success rate; contingency management has had efficacious effects in the substance misuse population.45

**E5.1 Control**

A control group would require an activity to avoid the confounding effects increased time, attention, and social interactions may have. De La Garza et al.41 did not disclose adherence rates to their passive sitting control group, but it would be unreasonable to expect patients to regularly attend such sessions for 1 year. Cutter et al.’s36 utilization of sedentary Wii games as their control group was well received by patients with similar adherence rates to the exergames. Colledge et al.46 similarly attempted to have their control group play board games, billiards, and paint. However, adherence was relatively poor with almost half of the group attending less than 20% of the sessions. Patients will ultimately attend activities they enjoy and a similar approach in heeding to their preferences in conjunction with contingency management will be prudent in increasing a time and attention control’s adherence rate.

**E5.2 Outcomes**

As previously mentioned though, buprenorphine’s efficacy is predicated on treatment adherence. Previous studies have logically operationalized buprenorphine adherence as treatment retention over a length of time either as a continuous or dichotomous variable. The definition of treatment retention in literature has predominantly revolved around attending physician visits47, 48 or having an active prescription within a certain time of a study’s end date. When considering study length, OUD must be recognized as a chronic illness with wavering periods of abstinence and relapse. Having too short of a study length may not accurately capture the essence of this
phenomenon. A study length of 1 year may be ideal as literature suggests significant benefits associated with a year of continuous buprenorphine use including decreased opioid use and opioid related hospitalizations. Though opioid use initially decreases with buprenorphine use in the first two months of use, it relapses until the 1-year mark when it continuously tapers down. Theoretically, guiding buprenorphine users past this time point gives them a better control of their illness, contributing to higher buprenorphine retention rates and ultimately, higher opioid abstinence rates.

Treatment adherence may also be measured by the percentage of times a patient takes buprenorphine. While this would be a more direct way in measuring adherence, there is no objective test to measure this. Current laboratory test can detect the presence of buprenorphine use, measuring total buprenorphine and its metabolite, norbuprenorphine. However, buprenorphine dose has not been shown to correspond well with either total buprenorphine or norbuprenorphine in any testing modality. Like other medications, buprenorphine is not immune to diversion and this should be accounted for.

The fundamental goal of buprenorphine is to improve functionality through eliciting opioid abstinence. While it is ideal, total abstinence is a poor functional outcome as the simple virtue of being on buprenorphine can be effective. Many studies measure opioid abstinence through negative opioid urine test. Although opioid urine test can objectively measure opioid abstinence, it comes with limitations. Opioid drug tests can generally only detect opioids within 3-4 days of use. Additionally, the frequency and quantity of opioid use is indiscernible. The Timeline Follow-Back instrument can complement a urine drug test and offset its limitations. Although it is self-reported measure, the Timeline Follow-Back instrument has been successful in many substance misuse studies with a high degree of validity, including opioid studies.
can be a severely debilitating illness, affecting multiple dimensions of health. Multiple health related quality of life surveys are available that aim to quantify these dimensions. The 36-item short form survey (SF-36) is one such survey, measuring 8 different dimensions of health to calculate a global measure of health. Th SF-36’s reliability and validity are well regarded and has been used as a quality of life measure in many different illnesses, including OUD.55

2.3 Conclusion

With the continued rise in the prevalence of OUD and low, unwavering buprenorphine retention rates, there is a need for a novel adjunctive therapy to buprenorphine. Although clinical trials allude to aerobic exercise’s efficacy in buprenorphine retention through hypoalgesia effects, sleep benefits, comorbid drug use reduction, and mental disorder reduction, the true relationship between the two variables remains to be established. A pilot RCT conducted by Cutter et al.36 showed underwhelming results, but had notable limitations. Despite these limitations, the study provided a strong structural template for future studies.

References
2. SAMHSA. Results from the 2018 National Survey on Drug Use and Health: Detailed Tables 2018.


Chapter 3: Study Methods

3.1 Study Design

We will conduct a single institution, multi-center, double arm, single blinded, parallel group, randomized controlled trial. Study subjects will include individuals with OUD entering opioid agonist therapy for the first time who are deemed appropriate for buprenorphine by a physician or midlevel provider. If they meet eligibility requirements (Figure 1) and give informed consent, they will undergo stratified randomization and be allocated to the intervention or control group.

The primary outcome, retention, will be measured at the end of the 1-year study as a dichotomous variable. Data related to secondary outcomes such as quality of life and number of missed buprenorphine doses will be collected at a monthly interval. To ensure patients are not diverting buprenorphine and are accurately self-reporting the number of missed buprenorphine doses, they will be required to consent to monthly drug urine measurements for buprenorphine metabolites throughout the study duration.

Figure 1: Eligibility Criteria

Inclusion

Age ≥ 18
Meet the DMS-5 criteria for OUD on assessment by a physician or midlevel provider
Ability to read/understand English.

Exclusion

Current use of opioid agonist therapy
Medical conditions or physical disabilities precluding the ability for regular aerobic exercise
Medical condition contraindicating the use of buprenorphine
Evidence of current suicidal or homicidal intentions
Bulimia or anorexia
History of seizures
Severe untreated psychiatric disorders
Diagnosis of a terminal disease that would preclude follow up at 1 year
3.2 Study Population and Sampling

The study population will compose of adults meeting the eligibility criteria from the two APT Foundation locations in the greater New Haven, Connecticut area and the Adult Primary Care Center at Yale New Haven Hospital – Saint Raphael’s Campus over a one year time period. The APT Foundation is a private non-profit organization specializing in treating patients with substance use disorders. It serves as a large federally regulated opioid treatment program that dispenses methadone and prescribes buprenorphine. The Primary Center of Yale New Haven Hospital provides office-based buprenorphine treatment and is staffed by attending and resident physicians that provides addiction recovery services in addition to comprehensive medical care. These two organizations will provide a diverse sample population reflective of the patients with OUD receiving treatment in the two most common types of settings.

It would be unethical to withhold opioid agonist therapy for an extended period as its mortality and morbidity benefits are overwhelmingly supported in literature. Thus, the 11 month recruitment period will be ongoing with weekly start dates. Individuals recruited and agreeable to the study will undergo randomization at the end of the week and start the 1-year trial on a rolling basis.

3.3 Recruitment

Eligible patients at the APT Foundation and Primary Care Center will be notified by front desk personnel on the details of the study. Eligible patients will also be handed a business card with the phone number of a presiding research assistant. Given the sequentially sensitive nature of the study, eligible patients will be approached right after the intake process if they are interested in participating to ensure they do not initiate buprenorphine until the study start date.
During the initial consultation session, a research assistant will elaborate on the rationale behind the intervention, the expectations of the study, and the time commitments required of the study. They will be informed of the possibility of having access to the intervention if they are to be randomized to the control group after conclusion of the study. Research assistants will emphasize that the study will not have any bearings on the requirements of either the APT Foundation or the Primary Care Center. Potential participants who are hesitant in agreeing to the study at that time may call the number provided on the business card to speak with a research assistant who will answer any lingering questions.

3.4 Subject Protection and Confidentiality

Prior to the recruitment period, this study will be proposed to the Human Investigation Committee of the Yale School of Medicine and the APT Foundation Board to gain Institutional Review Board approval. The proposal will include an extensive overview of each research staff member involved in the study with their respective status in Human Subjects Protection training and Health Insurance and Portability and Accountability Act (HIPAA) training. Documents such as informed consent form, any financial disclosures and study questionnaires will also be included in the proposal. The informed consent form will detail the goals of the study, time requirements of the study, and potential risks and benefits of the intervention. The study will only recruit literate English speaking individuals, removing the need for consent forms in different languages; a research assistant will orally present the details of the consent form to the patient who will also receive a copy of the consent form. At that time, the research assistant can help answer any of the patient’s questions regarding the study.
To maintain confidentiality, any patient medical information collected in this study will be stored on a secure server with added encryption software, only accessible to pertinent research personnel. To deidentify study participants in accordance with HIPPA, we will use the Safe Harbor method which removes 18 identifiers such as name, phone number, and social security number and assigns a unique ID number which becomes attached to all the patient’s study data. Paper files used in the study will be transferred onto the secure server and subsequently shredded.

3.5 Study Variables and Measures
A. Interventions

The intervention group will receive a yearlong aerobic exercise regime with the primary intent of increasing buprenorphine adherence while the control group will undergo a time and attention control. Patients in the intervention group will attend three one-hour sessions per week at Yale New Haven Health’s Livingwell Fitness Center. Multiple sessions a week will be scheduled to account for patient schedule flexibility and transportation will be provided. Given the study’s estimated sample size, sessions will be capped at 20 participants to allow for adequate room. Sessions will be led by an exercise physiologist and conducted in groups with two parallel sessions to account for different fitness levels; participants have the option to pick which session to attend prior to every session. A session will be composed of a 5 minute warmup, 40 minute conditioning, 5 minute cooldown, and 10 minute stretching phase in that order. Warmup, cooldown and stretching phases aim to ensure musculoskeletal longevity through increasing range of motion and reducing risk of injury.¹
B. Control

To control for the time and attention of the intervention group, the control group will attend three one-hour sessions per week as well and engage in a sedentary activity. The control group’s logistics will be identical to the intervention groups. A parallel session will still be held to give a wider range of activities in efforts to increase control adherence and for the logistical purpose of having the physical space to accommodate participants. Sessions will be led by activity coordinators and held in vacant Yale University buildings.

C. Standard Medication Management Care

Both study groups will continue to receive patient specific buprenorphine treatment throughout the duration of this study. The initial intake process in both the APT Foundation and the Primary Care Center at Yale New Haven Hospital involves a thorough psychosocial history performed by a clinician to evaluate if buprenorphine is appropriate for the patient. Patient specific adjunctive therapy at these sites accompanies buprenorphine induction; therapy may include a mixture of cognitive based therapy, motivational interviewing, 12-step counseling, etc. Buprenorphine will be offered as Suboxone, a sublingual film form that includes buprenorphine and naloxone as its active ingredients in a 4:1 ratio. Induction of buprenorphine and subsequent treatment doses will be based on the American Society of Addiction Medicine guidelines.\(^2\) During monthly follow-up meetings with the respective clinic, urine will be collected to evaluate drug misuse and buprenorphine adherence. In both groups, individuals will be told to refrain from aerobic exercise in their personal lives, but no other forms of health advice will be given.
D. Baseline Variables

Baseline demographics and clinical characteristics of both study groups will be compared. Such characteristics include age, sex, race, body-mass index, employment status, education level, illicit drug use, counseling hours, buprenorphine maintenance dose, major depressive disorder diagnosis and length of opioid use (Table 1).

Table 1: Baseline Patient Characteristics

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E. Primary and Secondary Outcomes

The primary outcome variable in this study will be the percentage of patients retained on buprenorphine treatment at 1 year. To be considered retained, participants must have been continuously in treatment and test positive for urine buprenorphine metabolites at the end of the year study. We will define continuous treatment as participants having an active buprenorphine prescription within 45 days and have communicated with the clinic within 45 days.³

Buprenorphine is typically prescribed as a monthly take home medication in stabilized patients, the extra 15 day grace period is to account for unforeseen circumstances (e.g. loss of insurance). Participants who fail to meet either of those criteria will be considered as not retained. Those lost
to follow up who desire to return to the study will be allowed if start dates remain. However, they will be considered as a new participant, time accrued before being lost to follow up will be nulled.

Secondary outcome variables include:

- **Number of opioid overdoses**
  - The number of opioid overdoses will be a self-reported number. Additionally, research assistants will check patients’ electronic medical records for any hospital visits concerning overdoses.

- **Amount of illicit drug and opioid use**
  - The amount of illicit drug and opioid use will be measured by a monthly Timeline Follow-back questionnaire. Substances of interest will include heroin, cocaine, alcohol, marijuana, and illicit opioids. Each participant will be asked to provide monthly total urine samples to verify these self-reported numbers. Temperature strips will be used as one measure to ensure urine samples are not adulterated or substituted.

- **Number of missed buprenorphine doses**
  - The number of missed buprenorphine doses will be a self-reported number. To ensure patients are not diverting buprenorphine and are accurately self-reporting the number of missed buprenorphine doses, monthly urine sample testing for buprenorphine and its metabolite, norbuprenorphine, will be collected. Patients with a buprenorphine level \( \geq 700 \text{ng/mL}^4 \) or a buprenorphine:norbuprenorphine ratio \( \geq 0.2^5 \) will be considered as nonadherent.
Quality of life

- This will be measured by the Medical Outcomes Study Short-Form 36 Health Survey. This 36-question survey asks questions pertaining to one’s physical and mental wellbeing with some questions being weighted more than others.

Table 2: Descriptive Analysis for Intervention vs Control

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**3.6 Methodological Considerations**

**A. Assignment of Intervention**

Enrolled patients will undergo stratified randomization through a computer to allocate a 1:1 intervention to control group ratio. Patients will be stratified on gender and race, two potential confounding variables observed in the literature. Gender will be a dichotomous stratum, either male or female; race will be a nominal stratum, grouped as White, Black, Hispanic, Asian and other. These classifications will be based on what is stated on electronic medical records. A single research assistant’s sole role will be to oversee randomization at all sites. After the randomization, the research assistant will communicate each patient’s study allocation to the onsite research assistants who will deliver sealed, opaque envelopes with a patient’s study allocation to the respective patient.

**B. Blinding of Intervention**
Due to the nature of this study, blinding of the intervention to the study groups is not possible. However, clinical staff at the APT Foundation and Adult Primary Care Center will be blinded of the patient’s study allocation. Patients in both study groups will be explicitly told not to disclose their group study allocation with their clinical team.

C. Blinding of Outcome

Research assistants administering surveys throughout the study measuring secondary outcomes will be unaware of patient’s study allocation. The research assistants involved with the assignment of intervention and the clinical staff at APT Foundation and Adult Primary Care Center will not be involved in assessing study outcomes.

D. Intervention Adherence

Patient attendance to assigned treatment arm will be recorded prior to the start of every session by the session leader; treatment adherence will be defined as attending a minimum of 80% of required sessions (124 out of 156 sessions). In efforts to increase adherence to the exercise intervention, a monthly survey with a list of aerobic exercises will be given to patients, allowing patients in effect, to vote for their specific type of intervention and continuously tailor activities to their preferences. Popular aerobic exercise types determined by the survey will be used as the intervention every week until the next survey results. The same procedure will be done for the control arm. After survey results are finalized, a monthly calendar will be distributed with a schedule of classes, ensuring patients are informed of activities and start times. Classes will be held in the morning and evening to accommodate patient obligations (work, childcare, etc.). Travel expenses will be reimbursed weekly to mitigate intervention nonadherence due to inaccessibility. To further encourage intervention adherence, patients will
be compensated $15 for attendance and weekly raffles for $150 will be held. A raffle ticket is earned by attending a session, bonus tickets are rewarded for attending consecutive sessions (e.g. attending all 3 required sessions in a week will grant an additional ticket).

As we are defining aerobic exercise as moderate intensity aerobic exercise, we will use Polar M200 watches to measure heart rate during exercise sessions. Maximal heart rate will be estimated using the Gellish equation: \( \text{HR}_{\text{Max}} = 207 - (0.7 \times \text{age}) \). Patients who fail to reach the ≥40% heart rate reserve threshold in the conditioning phase of the session will be notified and considered as if they were absent for the session. The Polar M200 is also capable of logging heart rate measurements which can be reviewed when the watch is connected to a computer. Patients who have sustained heart rate reserves >40% for ≥150 minutes per week outside of the intervention will be considered as nonadherent to study protocols. This exercise restriction outside allocated study time will be incentivized in both study arms with the benefit of keeping the watch after conclusion of the study for adherent patients.

Participants will be required to inform the research team if unanticipated events arise that preclude buprenorphine use or attendance to activity sessions. In addition, research assistants will check the National Death Index on a monthly basis in attempt to account for patients lost to follow up.

### 3.7 Data Collection

Primary and secondary outcomes will be collected within the 1-year study length. The primary outcome of retention will be measured at the end of the patient’s study duration. One of the secondary outcomes, quality of life, will be measured during intake and again at the conclusion of the study. Other secondary outcomes which include number of overdoses, number of missed buprenorphine doses, and amount of illicit drug and opioid use will be measured.
Research assistants will oversee administering questionnaires and surveys related to secondary outcomes and transfer data results over to the dedicated secure server. Baseline patient characteristics will hinge on those collected during the intake process by site clinicians.

### 3.8 Sample Size Calculation

This study’s design entails two-sided hypothesis testing, an alpha of 5% and power of 80%. Using 49.45% as the current 1-year buprenorphine treatment retention rate, to detect an effect size of more than a 17.55% increase in percentage of participants in the intervention group retained in treatment at 1 year, a total sample size of 270 participants will be needed given an enrollment ratio of 1. The current 1-year buprenorphine retention rate is based off the average 1-year retention rate observed in 2 relatively recent studies done in urban cities with similar demographics and definition of retention to the one proposed by this study.\(^3\),\(^7\) Effect size was measured by the difference between the current 1-year buprenorphine treatment retention rate and that of the 1-year buprenorphine treatment retention rate of Boston Medical Center's Office Based Addiction Treatment Program (67%). The program reports one of the highest retention rates in a Northeast urban city, innovatively using nurse care managers to aid in buprenorphine treatment delivery.\(^8\) An attrition rate of 10% is accounted for in this sample size calculation based off previous studies using exercise as an intervention in the context of substance use.\(^9\),\(^10\)

### 3.9 Statistical Analysis
Baseline patient characteristics will be compared between the two study arms using chi square test for proportions of categorical variables and independent t-test for normally distributed continuous variables (Table 1).

The primary outcome of retention will be evaluated with a chi square test. If baseline characteristics prove to be unequal even after randomization, retention will be evaluated with a multivariate regression instead. Secondary outcomes including the amount of illicit drug and opioid use and number of missed buprenorphine doses will be evaluated with independent t-tests. Quality of life will be measured with a paired t-test.

Statistical analysis will follow an intention to treat analysis with statistical significance defined as \( p < 0.05 \).

### 3.10 Timeline and Resources

The study will begin its 11 month rolling basis recruitment on January 4, 2021. Each patient is expected to be in the study for a year. Patients lost to follow up who wish to reenroll in the study may do so only within the recruitment period. The study will conclude in 2 years on January 4, 2023 with data collection and statistical analysis completed within the time frame.

Personnel required in this study include 5 research assistants, 4 certified strength and conditioning specialist and 4 activity coordinators. Each of the three clinical sites will have its own exclusive research assistant. One research assistant will oversee the randomization process while another oversees administration of questionnaires and surveys.

Essential locations include Yale New Haven Health’s Livingwell Fitness Center and Yale University classrooms. We will request access to these areas for the purposes of this study prior to the study’s start date.
References


Chapter 4: Conclusion

4.1 Strengths and Advantages

Our proposed study will be the first of its kind to explore the efficacy of aerobic exercise in buprenorphine retention. Other than its novelty, the primary strength of our study lies in the design of our intervention in accordance with American College of Sports Medicine guidelines and the use of a time and attention control. Its flexible and preferential structure in addition to the use of contingency management aims to ensure adequate intervention and control adherence rates. Additionally, our study’s methodology promotes internal validity. Stratified randomization and allocation concealment will limit selection bias and ensure similar baseline characteristics in potential confounding variables. Blinding of clinicians and interviewers will prevent detection and observer bias.

A multi-center approach provides a large population to draw from; previous studies involving exercise and substance use are often limited by a low sample size. The use of a private organization and a major teaching hospital will give us access to a diverse patient population.

4.2 Limitations and Disadvantages

Although our study design minimizes selection bias, the very nature of the intervention leads to unavoidable areas of bias. As enrollment is voluntary, many patients who choose to enroll already have a predilection towards aerobic exercise. This limits external validity and given that blinding patients is impossible, introduces bias into the study as patients may have a favorable belief of aerobic exercise. We are likely to lose patients who are randomized to the control arm due to the desire to exercise. Even though we will be offering the intervention to these patients after completion of the study, we acknowledge the additional time commitment it
would entail. Furthermore, studies who have high exercise adherence rates with the utilization of contingency management were relatively short in duration. It remains unestablished how adherent patients will be in a year long study and it would be reasonable to expect some levels of nonadherence in both study arms. The financial cost of contingency management over a full year will be significant in addition to the salaries of the study staff. Finally, although the Polar M200 watch can theoretically monitor aerobic exercise outside of the allocated study time, patients may still find ways to exercise undetected, such as having another person wear the watch for them.

It should also be acknowledged that patients leave buprenorphine treatment for reasons other than relapse. Such reasons include disagreements with a treatment program’s structure and involuntary discharge due to financial restrictions, incarceration, and failing to meet program obligations.\(^1\) These are all aspects that contribute to buprenorphine’s low retention rate and areas that aerobic exercise cannot rectify.

### 4.3 Clinical and Public Health Significance

OUD remains a major public health emergency associated with severe morbidity and mortality. However, the battle against the opioid epidemic has gained significant traction in the past few years with political involvement and increased funding. Most recent surveyed data by SAMSHA shows the total number of patients with OUD decreased from 2.1 to 2 million people between 2017 and 2018\(^2\) and more people were treated with opioid agonist therapy. Although this is a step in the right direction, we must recognize the gaps in the current standard of care to further progress in this endeavor. Buprenorphine is a safe and effective drug for OUD with low retention rates. Aerobic exercise has been shown in theory to alleviate this issue. This study
seeks to explore its efficacy in practice and if successful, change the way clinicians approach OUD.

References


2. SAMHSA. Results from the 2018 National Survey on Drug Use and Health: Detailed Tables 2018.
## Appendix A: Timeline Followback

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### TIMELINE FOLLOWBACK CALENDAR: 2021

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Appendix B: 36-Item Short Form Survey

SF-36 QUESTIONNAIRE

Name:____________________ Ref. Dr:___________________ Date: _______
ID#: _______________ Age: _______ Gender: M / F

Please answer the 36 questions of the Health Survey completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

Compared to one year ago, how would you rate your health in general now?

☐ Much better now than one year ago
☐ Somewhat better now than one year ago
☐ About the same
☐ Somewhat worse now than one year ago
☐ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Lifting or carrying groceries

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing several flights of stairs

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing one flight of stairs

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bending, kneeling, or stooping

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking more than a mile

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking several blocks

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all
Bathing or dressing yourself
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐

PHYSICAL HEALTH PROBLEMS:
No, Not Limited at all
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
☐ Yes ☐ No

Accomplished less than you would like
☐ Yes ☐ No

Were limited in the kind of work or other activities
☐ Yes ☐ No

Had difficulty performing the work or other activities (for example, it took extra effort)
☐ Yes ☐ No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
☐ Yes ☐ No

Accomplished less than you would like
☐ Yes ☐ No

Didn't do work or other activities as carefully as usual
☐ Yes ☐ No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
☐ Not at all ☐ Slightly ☐ Moderately ☐ Severe ☐ Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?
☐ None ☐ Very Mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

**Did you feel full of pep?**
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

**Have you been a very nervous person?**
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

**Have you felt so down in the dumps that nothing could cheer you up?**
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

**Have you felt calm and peaceful?**
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

**Did you have a lot of energy?**
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have
Have you felt downhearted and blue?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Did you feel worn out?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Have you been a happy person?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Did you feel tired? All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
<table>
<thead>
<tr>
<th>Time Options</th>
<th>General Health Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the time</td>
<td>I seem to get sick a little easier than other people</td>
</tr>
<tr>
<td>Most of the time</td>
<td>I am as healthy as anybody I know</td>
</tr>
<tr>
<td>Some of the time</td>
<td>I expect my health to get worse</td>
</tr>
<tr>
<td>A little bit of the time</td>
<td>My health is excellent</td>
</tr>
<tr>
<td>None of the time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>How true or false is each of the following statements for you?</td>
</tr>
</tbody>
</table>

1. I seem to get sick a little easier than other people
   - Definitely true
   - Mostly true
   - Don't know
   - Mostly false
   - Definitely false

2. I am as healthy as anybody I know
   - Definitely true
   - Mostly true
   - Don't know
   - Mostly false
   - Definitely false

3. I expect my health to get worse
   - Definitely true
   - Mostly true
   - Don't know
   - Mostly false
   - Definitely false

4. My health is excellent
   - Definitely true
   - Mostly true
   - Don't know
   - Mostly false
   - Definitely false
Hi, my name is Timothy Fong and I am a Physician Associate student from Yale School of Medicine. I am conducting a research study to examine the effect of aerobic exercise on buprenorphine adherence. Participation in this study will involve either partaking in group aerobic exercise classes or group sedentary activities. Your involvement will require 3 hours a week for one year. You will receive $15 per session you attend with the chance to participate in weekly raffles for additional monetary prizes.

You may experience musculoskeletal injuries and in rare cases, arrhythmias, sudden cardiac arrest, and myocardial infarctions. We hope this study will support you through your opioid use disorder by improving your general wellbeing. We hope that our results will add to the knowledge about the effects of aerobic exercise has on buprenorphine adherence.

All of your responses will be held anonymous. Only the researchers involved in this study and those responsible for research oversight will have access to the information you provide. Your responses will be handwritten or performed over the computer.

Your responses will be linked to a unique ID number and stored on a secure server with added encryption software. Any study results written on paper will be shredded after being transferred to the server. The information you provide will eventually be destroyed after publication of the study.

Participation in this study is completely voluntary. You are free to decline to participate, to end participation at any time for any reason. Your decision whether or not to participate in this study will not affect your relationship with the APT Foundation, Adult Primary Care Center, or Yale School of Medicine.

If you have any questions about this study, you may contact the investigator, Timothy Fong at 203-570-5060 or Dr. David Fiellin at 203-688-4516.
If you would like to talk with someone other than the researchers to discuss problems or concerns, to discuss situations in the event that a member of the research team is not available, or to discuss your rights as a research participant, you may contact the Yale University Human Subjects Committee, 203-785-4688, human.subjects@yale.edu. Additional information is available at https://your.yale.edu/research-support/human-research/research-participants/rights-research-participant

Do you have any questions at this time? Would you like to participate in the study?
## Appendix D: Sample Size Calculation

### Dichotomous Endpoint, Two Independent Sample Study

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Study Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td>Incidence, group 1</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td>Incidence, group 2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
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</tr>
<tr>
<td></td>
<td>Beta</td>
</tr>
<tr>
<td></td>
<td>Power</td>
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</table>

<table>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>123</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>246</strong></td>
</tr>
</tbody>
</table>

4. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database of Systematic Reviews. 2011(10)


67. SAMHSA. Results from the 2018 National Survey on Drug Use and Health: Detailed Tables 2018.


