Aerobic Exercise Interventions for Patients in Opioid Maintenance Treatment: A Systematic Review

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ABSTRACT

BACKGROUND: Opioid maintenance treatment (OMT) is the standard for treatment of opioid use disorder, but some individuals on OMT experience disrupted sleep, heightened sensitivity to pain, and continued relapse to non-medical opioid use. An adjunctive treatment that has potential to address these shortcomings of OMT is aerobic exercise.

OBJECTIVE: The aim of the present review was to identify and evaluate components of aerobic exercise interventions targeting OMT patients.

METHODS: For this PROSPERO-registered review (ID CRD42020139626), studies were identified via electronic bibliographic databases, funded research (*NIH RePORTER*) and clinical trials databases (*ClinicalTrials.gov*), and reference sections of relevant manuscripts. Studies that evaluated the effects of an aerobic exercise intervention using a comparison condition or pretest-posttest design in adult OMT patients were included.

RESULTS: Of 2971 unique records, three primary studies and one supplemental manuscript comprised the final sample. All studies were randomized trials involving supervised exercise interventions enrolling small samples of middle-aged OMT patients. Exercise interventions included a variety of aerobic and non-aerobic activities (e.g. flexibility exercises), and none controlled the dose of aerobic exercise. Few studies used objective measures of physical activity or cardiorespiratory fitness and there were no significant effects of adjunctive exercise on substance use outcomes, but tests of the latter were likely underpowered.

CONCLUSIONS: Though early in the accumulation of evidence, interventions targeting aerobic exercise for OMT patients appear feasible, acceptable to patients, and beneficial. Longer-term studies that employ larger samples, include assessments of behavioral and biological mechanisms of change, more rigorous measurement of physical activity, and controlled doses of aerobic activity are warranted.

KEYWORDS: aerobic exercise, physical activity, opioid use, opioid maintenance treatment, methadone maintenance treatment

Despite the increased visibility of the opioid epidemic, non-medical opioid use continues to operate as a major source of mortality and morbidity in the United States. An estimated 10.3 million individuals 12 years of age and older used heroin or prescription opioids in 2018[1] and deaths due to opioid drug overdose rose four-fold from 2002 to 2017.[2] Not surprisingly, the number of individuals entering substance use treatment for opioids has also increased through this time; and as of 2015, opioids have become—and continue to be—the most commonly used substance for those entering publicly-funded substance use treatment.[3]

Opioid maintenance treatment (OMT) is a pharmacotherapy for opioid use disorder (OUD) and is one of the most effective OUD treatments to date.[4] The goal of OMT is to reduce opioid craving and withdrawal, and in so doing, reduce non-medical opioid use and associated risky behaviors (e.g. needle sharing). Although OMT is the standard care for OUD, many OMT patients experience challenges such as chronic pain,[5] heightened sensitivity to pain[6–8] (hyperalgesia), disrupted sleep,[9–11] and weight gain[12] (but see Peles et al.[13]). Critically, pain and sleep disturbance may be important targets in preventing relapse to opioid use.[14–16] Further, maintaining a healthy weight is important to general health and quality of life (e.g. reduced risk of cardiovascular disease, increased physical ability and longevity). Thus, despite its benefits, OMT alone falls short as a comprehensive treatment. At present, there are no existing treatments that simultaneously improve pain, sleep, and weight outcomes among patients on OMT.

A targeted adjunctive treatment with potential to improve OMT outcomes is a supervised aerobic exercise regimen. Aerobic exercise has been proposed as a treatment for substance use based on preclinical support from a variety of models of human drug taking (e.g. acquisition of drug self-administration, maintenance, and relapse; see Smith and Lynch[17] for review). In the case of opioids, aerobic exercise reduces self-administration of morphine[18] and heroin[19] in rats, in addition to attenuating symptoms of physical dependence on morphine (e.g. anxiety, depressive-like behavior) in a rat model of OMT.[20] In humans, there is preliminary support for the utility of aerobic exercise in treating substance use generally based on epidemiological and initial clinical outcomes data (see Abrantes and Blevins[21] and Wang et al.[22] for reviews and meta-analysis). The benefits of aerobic exercise render it particularly well suited to address the shortcomings of OMT,[23] in that it reduces pain symptoms,[24] improves sleep quality,[25,26] and is critical for maintenance of healthy weight.[27]

Several observational and self-report studies also support the acceptability and potential of adjunctive exercise interventions to improve OMT outcomes. For example, one study[28] showed that individuals seeking methadone maintenance treatment reported no moderate or vigorous intensity physical activity in the past week, while 24% reported interest in exercise group participation. Participants who met recommended levels of physical activity in the past week had significantly lower levels of depression compared to participants that did not. Complementary to these findings, another study[29] reported that methadone-maintained patients were willing to consider physical exercise as a treatment for stress, with reasonably high perceived efficacy of exercise.

In a self-report study[30] examining perceived benefits and barriers to exercise among methadone maintained patients, many perceived more benefits of exercise relative to barriers. However, only 38% met recommended guidelines for physical activity, and 25% reported no physical activity. Those who did meet recommended physical activity guidelines endorsed relapse prevention as a benefit to exercise more often. In broader substance use treatment populations (not limited to treatment for OUD or OMT patients), inactivity is associated with poor quality of life indicators among men.[31] These findings align with others showing that depression was significantly and positively related to higher sitting time (i.e. inactivity) among methadone maintained smokers.[32]

In a qualitative study assessing factors associated with relapse among former and relapsed heroin users (including both those who had and had not utilized OMT services),[33] several participants reported exercise (in addition to other factors) as a method to reduce likelihood of relapse. These participants reported that exercise facilitated heroin cessation by serving as a diversion tactic, an enjoyable activity, and leading to increased discipline. Participants reported diverse exercise activities including *tai chi*, soccer, basketball, weight lifting, running, and walking.

While aerobic exercise as an adjunctive treatment to OMT appears promising, few controlled laboratory human clinical trials have been conducted to test its efficacy. At present, little if any data inform biological and mechanistic contributions of exercise as an adjunctive treatment to pharmacotherapy within OUD populations. There is also a lack of understanding of how to effectively implement an aerobic exercise intervention within OMT populations, or how much or what type of exercise might be most beneficial. The purpose of the present systematic review was to identify existing published studies and synthesize the methods employed in studies evaluating OMT plus aerobic activity on OUD and health outcomes. The primary focus of this review was to present intervention characteristics employed (e.g. exercise dose, type). Secondary aims were to describe study design and sample characteristics. Results of this review will help inform future research in the development and refinement of clinical protocols that effectively leverage the benefits of aerobic activity in providing a comprehensive treatment for OUD.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review.[34] The PRISMA 2009 Checklist can be found in the supplementary materials (Table S1). This review was pre-registered with PROSPERO (ID CRD42020139626), an International Prospective Register of Systematic Reviews, prior to data extraction.

Inclusion criteria, information sources, and search strategy

Multiple strategies were used to identify relevant studies. First, four electronic bibliographic databases (PubMed, PsycINFO, SCOPUS and Cochrane Library) were searched using a Boolean search strategy and database-specific terms. For example, the PubMed search string was: [(((((((((opioid[MeSH Terms]) OR "opioid abuse") OR "opioid dependence") OR "opioid addiction")) OR "opioid maintenance treatment") OR "opioid maintenance therapy")) AND ((((exercise) OR aerobic) OR "physical activity") OR walking)]. All database searches retrieved published (print or electronic) reports through December 10th, 2018. Second, the references of identified relevant reviews and other related manuscripts retrieved from our searches were reviewed. Third, *NIH RePORTER* (a database of funded research) and *ClinicalTrials.gov* were also reviewed to identify relevant trials and to pull related publications for review. Studies were included if they: (a) evaluated an aerobic exercise intervention, (b) included a comparison condition or pretest-posttest measures and (c) sampled adult patients currently enrolled in an OMT. Exclusion criteria included

book chapters, editorials, other systematic reviews and meta-analyses, theses and dissertations, cross-sectional studies, case studies and observational studies or studies that (a) did not include an aerobic exercise intervention and (b) did not include patients enrolled in an OMT.

Study selection

All identified records retrieved from the electronic bibliographic database searches were imported into EndNote X8, where duplicates were identified and removed. All of the remaining records were screened for inclusion by a trained reviewer (MLD) based on title and abstract. Records that needed to be screened more closely to determine eligibility and relevant systematic reviews had full text manuscripts retrieved and reviewed (MLD), then verified by a second reviewer (DJS). Studies that reported the same sample across multiple manuscripts were linked in EndNote X8 and are represented as a single study ID. The manuscript reporting the most complete data was selected as the primary manuscript while additional manuscripts on that sample were considered supplemental.

Data collection process and reliability

Two independent coders (MB, DJS) extracted study information, sample characteristics, and intervention details from the included manuscripts using an extraction form. This form was developed and pilot tested by the study team. Inter-rater reliability was assessed on variables captured in the extraction form (e.g. study, sample and intervention characteristics). The data extraction form contained both categorical and continuous variables as well as open text responses. Due to the variability in the scales of measurement across variables, the authors calculated percent agreement. Coders agreed on 96% of the judgements across categories (range = 94-98%; median = 95%). Discrepancies were discussed between the two coders until agreement was reached.

Study outcomes

The main outcomes were intervention details (e.g. dose, exercise components, delivery of program) of the included studies. Secondary outcomes included study information (e.g. design, location, and measurement details) and sample characteristics (e.g. baseline physical activity level, other substance use). Results are reported as aggregate data across included studies. Meaning, we report our findings quantitatively, as well as in a narrative synthesis. Methodological quality and risk of bias were not assessed in this review.

Results

Study selection

Searches of the electronic databases identified 2971 unique records. Reviews of *NIH RePORTER* and *ClinicalTrials.gov*

identified 3 and 2 related studies respectively, although these trials were ongoing or did not have any available results (and thus were not included). A total of 2670 records were excluded based on review of title and abstract. An additional 297 studies were excluded after full text review (see Figure 1). The final sample included three primary studies and one supplemental manuscript that provided additional information. Study, sample, and intervention characteristics for the three included studies are in Table 1.

Study and sample characteristics

Studies were published between 2007 and 2017 and originated in Spain (n = 1), Switzerland (n = 1) and the United States (n = 1). All studies were randomized trials with small samples (n = 27-29) of middle-aged (42 ± 4 years old) OMT patients that were predominantly male (68 ± 30%). Patients were recruited for participation through the clinic or community-based centers where they were receiving OMT (n = 2) or through the medical database of a penitentiary center (n = 1) where they were being treated. Baseline drug use measures were only reported for two of three studies. Further details of the study samples are in Table 1.

Intervention characteristics

No study included an intervention that was composed solely of aerobic exercise (i.e. they also included strength or other exercise components as well). Thus, the reviewed studies may be considered as employing exercise interventions more generally. Exercise interventions were conducted in a supervised setting and included a variety of aerobic (e.g. walking, dancing, biking, boxing) and non-aerobic (e.g. weight lifting, climbing, yoga, stretching) activities. None of the included studies stated use of behavioral theory to inform development of study materials or design. With regard to dose of exercise, all studies reported the number of sessions in the intervention (range n = 23-48), and two studies reported the length of sessions (range n = 23-90 minutes) and frequency of sessions per week (range n = 2-5). Due to the variability in both type and amount of activity across sessions in the three studies, none can be classified as prescribing a controlled dose of aerobic exercise specifically. There was considerable variation in the definition and reporting of intervention adherence: one study did not report adherence, another reported that 38% of participants missed fewer than 5 of 23 sessions, and the remaining study reported that 63% of intervention sessions were completed.

Physical fitness and physical activity outcomes

Limited measures of physical fitness and objective physical activity were obtained in the included studies. The only study directly assessing physical fitness measured the impact of the exercise intervention using objectively measured
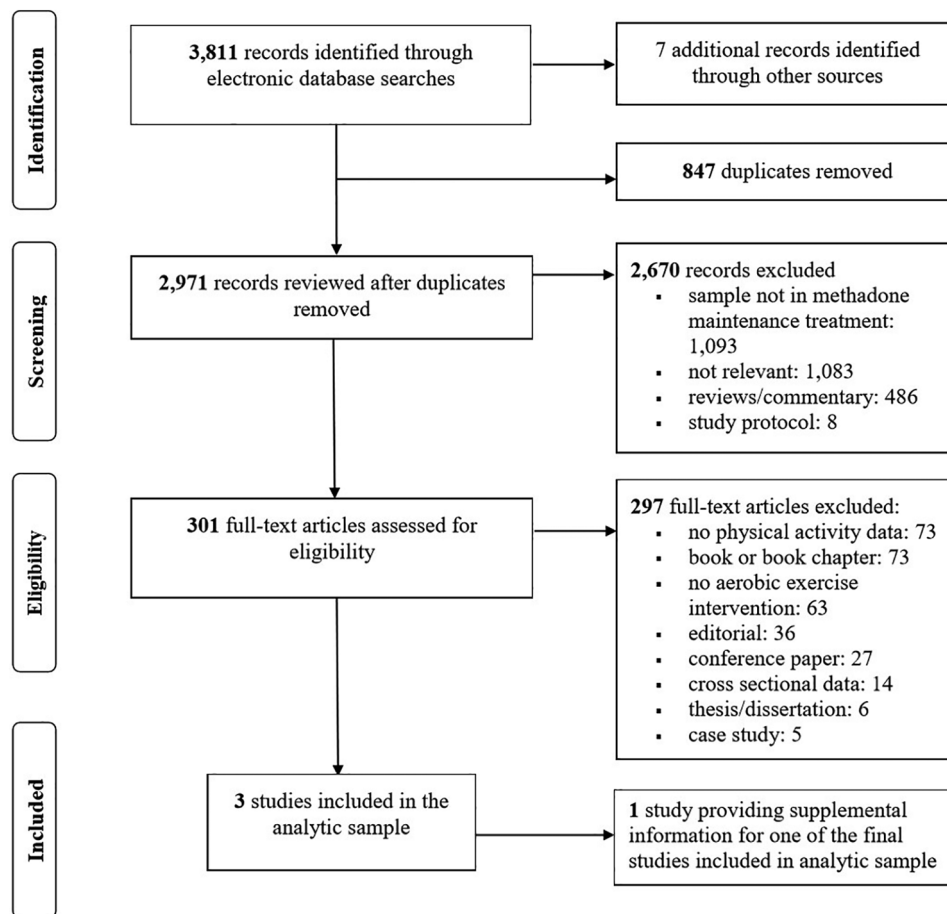
Figure 1. Screening and selection procedures for identifying articles to be included in the review and the number of articles meeting different criteria at each phase.

pre- and post-measurements of cardiorespiratory fitness (peak completed workload during the cardiorespiratory test, peak heart rate (HRpeak) and decline in heart rate at 1 min post-exercise), lower and upper body dynamic strength endurance, and muscle mass. In terms of extra-session physical activity, one study assessed self-reported physical activity with the International Physical Activity Questionnaire (IPAQ) Short Form, and another using the IPAQ Long Form. The most objective assessment of physical activity was obtained within-session (i.e. more of a manipulation check than outcome) using estimated exercise intensity based on Wii Fit calculations.

Feasibility, acceptability, and concurrent health and OMT outcomes

Though the focus of the original coding for this review was on the methods used in the included studies, outcomes of the studies are summarized here (coded by MD and spot checked by DJS). A wide range of outcome measures were assessed across each study. These measures included quality of life and fitness levels (e.g. HRPeak, muscle mass, blood pressure; Colledge et al.[35]; Perez-Moreno et al.[38]), feasibility, acceptability, and

substance use (Colledge et al.[35]; Cutter et al.[37]), psychological health (e.g. perceived stress, depressive symptoms; Colledge et al.[35]; Cutter et al.[37]), and self-reported sleep (Colledge et al.[35]). Retention in the three studies ranged from 70-93% (average 83%).

For the primary outcome measures reported in Perez-Moreno et al.,[38] quality of life significantly increased in the exercise group but not the control group, and cardiorespiratory and dynamic strength tests showed improvements in the exercise but not the control group. Cutter et al.[37] reported acceptability of the exercise intervention as high. Further, participants in the exercise versus control condition self-reported higher levels of physical activity outside of the supervised exercise sessions, although substance use or psychological wellness measures did not differ between the exercise and control groups. Finally, Colledge et al.[35] reported overall higher compliance with the protocol, and increased high intensity minutes exercising and grip strength in the exercise compared to the control group. No significant interaction effects of time by group were observed on psychological health or substance use measures (indicating that over the course of the intervention, exercise versus control conditions did not result in differences in these outcomes measures).

Table 1. Study, sample, and intervention characteristics of the studies (n = 3) included in systematic review.

STUDY	SAMPLE AND RECRUITMENT	BASELINE DRUG USE[a] M (SD) OR %	INTERVENTION AND CONTROL PROCEDURES	SESSION ACTIVITIES	SESSION IMPLEMENTATION	ADHERENCE[b]	PHYSICAL ACTIVITY MEASUREMENT	OUTCOMES
Colledge et al.[35] *Suppl. Study:* Staub et al.[36]	Sample Size: • Eligible = 50 • Enrolled = 28 (56%) • Retained = 24 (86%) Demographics: • 38% F • M_{age} = 44 Recruitment: Heroin-assisted treatment (HAT) clinic Location: Basel, Switzerland	Exercise: 0.23 (0.59) days of illicit heroin use 1.38 (2.21) days of cocaine use ICM: 0.20 (0.42) days of illicit heroin use 3.00 (8.80) days of cocaine use	Exercise: Face-to-face, instructor-led evening exercise sessions post-HAT. One weekly session involved moderate to vigorous activity and the other lower intensity activity. ICM: Face to face activities, designed to control for contact time with staff and access to alternative activities. Timing of HAT NR.	Exercise: Aerobic (walking, badminton, boxing, dance) or non-aerobic (climbing, strength training, coordination games). ICM: Board games, painting, cooking, museum visits, and billiard games.	Frequency: 2×/week Number: 23 Duration: NR	Definition: Categorized based on % sessions completed Obtained: 38%, ≥ 80% 54%, > 20% & < 80% 8%, ≤ 20%	In-Session: • None Extra-session*: • IPAQ short form	Feasibility: • None Acceptability: • None Psych. Health:* • Depressive symptoms • Sleep • Self-control • Perceived stress • Quality of life Phys. health: • Physical activity* • Blood pressure • Grip strength Substance use:* • Heroin • Cocaine • Alcohol • Cigarettes • Illicit RX
Cutter et al.[37]	Sample Size: • Eligible = NR • Enrolled = 29 (CNC) • Retained = 27 (93%) Demographics: • 59% F • M_{age} = 44 • 17% legal probation Recruitment: Non-profit, community-based TX organization Location: Connecticut, USA	SC + Exercise: 2.7 (7.1) days of opioid use 12.6 (12.3) days of cocaine use SC + ICM: 0.4 (0.9) days of opioid use 4.3 (6.5) days of cocaine use	SC + Exercise: Daily MMT and monthly group counseling. Participants also engaged in Wii Fit Plus exercises. SC + ICM: Daily MMT and monthly group counseling. Participants also played Wii games requiring minimal physical exertion.	SC + Exercise: Participant choice of two aerobic (e.g. basic run, hula hoop) and three non-aerobic games (strength, balance, yoga). SC + ICM: Participant choice of engaging Wii games that allow sitting	Frequency: 5×/week Number: 40 Duration: 20-25 min	Definition: % sessions completed Obtained: 63%	In-Session: • Wii Fit estimates (as kcals and METs) Extra-session*: • IPAQ long form	Feasibility: • Adherence • Retention Acceptability*: • Satisfaction with intervention Energy Expenditure: • Physical activity (extra-session)* • Estimated kcal (in-session) Substance use: • Alcohol* • Other drug use* • Cocaine • Morphine • Oxycodone Psychological Health*: • Perceived stress • Optimism • Psychiatric symptomology • Life satisfaction
Pérez-Moreno et al.[38]	Sample Size: • Eligible = 31 • Enrolled = 27 (87%) • Retained = 19 (70%) Demographics: • 0% F • M_{age} = 37 • 100% incarcerated Recruitment: Penitentiary center Location: Madrid, Spain	Exercise: NR SC: NR	Exercise: Supervised weekly exercise training sessions for 4 months SC: NR	Exercise: Aerobic training (biking) and non-aerobic training (weight lifting, crunches, stretching and flexibility exercises). SC: NR	Frequency: 3×/week Number: 48 Duration: 90 min	NR	In-Session: • Aerobic activity based on HR Extra-Session: • None	Quality of life* Fitness: • Cardio respiratory fitness (peak workload during cardiorespiratory test; HRpeak; decline in HR at 1 min post-exercise) • Lower and upper body dynamic strength endurance • Muscle mass

Note: CNC, could not calculate; F, female; HAT, heroin-assisted treatment; HR, heart rate; HRpeak, peak heart rate; ICM, irrelevant content matched; IPAQ, International Physical Activity Questionnaire; M, mean; METs, metabolic equivalent of tasks; MMT, methadone maintenance treatment; NR, not/none reported; RX, prescription; SC, standard of care; SD, standard deviation; TX, treatment.
[a]Self-reported current (last 30 days) drug use. [b]Intervention adherence. *Denotes that either a category of measures or a single measure was self-reported.

Discussion

To date, there are few studies evaluating the addition of an exercise regimen as an adjunct to OMT—let alone interventions evaluating effects of aerobic exercise specifically. Of those that have, there was substantial variability in the implementation of the regimens, the type and amount of aerobic exercise involved and, while some have based their prescription on published guidelines (e.g. Cutter et al.[37]) none appear directly rooted in theory (i.e. informed by theories pertaining to motivational or biological processes). In tandem, none investigated relevant underlying mechanisms of change that might contribute to improved health outcomes among OMT patients. Logistical constraints (e.g. participant schedules, preference) may contribute to the variability in the parameters of intervention implementation such as the number of sessions (ranging from 23 to 48), dose (23-90 minutes), and types of exercise participants engage in (both across and within identified studies). On the one hand, this variability makes it difficult to determine what aspects are key to developing a successful adjunctive aerobic exercise intervention; but on the other hand, some of the uniform successes in spite of this variability (e.g. average retention of 83%) support its potential utility.

In some cases variability in the intervention methods was driven by recommendations in physical activity (e.g. Cutter et al.[37]) but for others it was to accommodate participants' preferred modes (e.g. Colledge et al.[35]). Both are important considerations, as different activity types afford different benefits to health and physical fitness (e.g., resistance training improving bone mass vs. aerobic activity increasing cardiovascular fitness; see Garber et al.[39] for review) and there are individual differences in the reinforcing value of different modes of exercise.[40] The latter is related to how much individuals engage in different types of physical activities and thus may be a relevant factor for promoting adherence. Carefully designing intervention content based on participants' preferences (similar to Colledge et al.[35]; see also Staub et al.[36])—while keeping in mind the type, intensity, and duration of physical activity necessary to acquire its sleep, pain, and affective benefits—is imperative for future research. In other words, future interventions will benefit from the conjoint and direct consideration of both theory (e.g. behavioral principles of reinforcement) and empirical guidelines in their design.

There is also need for quantification of participants' adherence to activity prescription within-session. The way within-session activity has been assessed varies (e.g. based on percentage of heart rate maximum or use of technology to record activity as it naturally occurred, Pérez-Moreno et al.[38]; Cutter et al.[37]), if it is done at all.[35] Ensuring activity is accurately measured will provide a finer-grained assessment of adherence that can be used in analyses of outcomes; and will also be helpful in isolating the effects of aerobic exercise vs. physical activity or multi-modal exercise more generally. Extra-experimental physical activity has also been neglected from direct measurement, although two studies included a self-report measure.[35,37]

Given the increasing capabilities of fitness trackers (e.g., measuring heart rate, recording sleep) and their affordability, future research on adjunctive exercise interventions may benefit from their incorporation as tools for tracking activity both in and outside of sessions (for the latter, to assess and control for diffuse intervention effects and/or reactivity). However, the type of information and the specific device used should be chosen judiciously, as some have poorer accuracy than others (e.g. Thiebaud et al.[41]). As well, it will be critical to select and report on the specifics of measurement and adherence protocols used with devices to ensure accuracy and replicability of findings.[42]

Future research will need to assess the behavioral and biological mechanisms of aerobic exercise treatment effects and employ larger samples to clarify their role statistically. Laboratory studies have shown exercise to significantly impact drug-related variables such as cigarette[43] and alcohol craving[44] and nicotine withdrawal symptoms.[45] Similar findings with drug-related variables in OUD have been found in preclinical[22] and clinical research; although it is unclear in the latter case if exercise was delivered conjoint with a pharmacotherapy. Regardless, non-drug related mechanisms of particular interest to the present review in OMT populations (e.g. sleep and pain, pain sensitivity) have been assessed inconsistently and subjectively; and mechanisms untouched. The studies reviewed herein focused on development and feasibility[35,37] and improving health and fitness generally[38] in relatively small sample sizes (n = 27-29). As such, there was reasonably less focus on (and power to assess) these additional outcomes and mechanisms.

In conclusion, aerobic exercise appears uniquely situated to improve health and wellness features of those undergoing OMT, but much work remains to be done in its development as an intervention. In particular, there is a need for studies with more standardized intervention content (i.e. aerobic exercise type, duration, and intensity), increased statistical power, and assessment of the mechanisms responsible for treatment effects. It will also be important to examine the feasibility of such adjunctive interventions with various types of OMTs (e.g. OMTs requiring in-clinic visits for doses [methadone] vs. those taken at home [buprenorphine]) and other types of physical activity that may confer a similar constellation of physical benefits (e.g. yoga or resistance training). As the toll of the opioid epidemic persists, continued research on ways to improve OUD treatment is critical, in addition to addressing the structural and financial barriers of OMT itself.

Author contribution
DEJS: Conceptualization, Methodology, Investigation, Project Administration, Supervision, Data Interpretation, Writing – Original Draft. MSB: Conceptualization, Methodology, Investigation, Project Administration, Supervision, Data Interpretation, Writing - Original Draft. MLD: Methodology,

Investigation, Data Curation, Visualization, Writing- Review & Editing. DDC: Data Interpretation, Writing – Review & Editing. JD: Data Interpretation, Writing – Review & Editing. JMR: Data Interpretation, Visualization, Writing – Original Draft.

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Supplemental material
Supplemental material for this article is available online.

REFERENCES

1. Center for Behavioral Health Statistics and Quality. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health.* Rockville, MD; 2019. https://www.samhsa.gov/data/report/2018-nsduh-annual-national-report
2. National Institute on Drug Abuse. Overdose death rates. 2019. https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed September 16, 2019.
3. Center for Behavioral Health Statistics and Quality. *Treatment Episode Data Set (TEDS): 2017. Admissions to and Discharges from Publicly-Funded Substance Use Treatment.* Rockville, MD; 2019. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/TEDS-2017.pdf
4. Connery HS. Medication-assisted treatment of opioid use disorder. *Harv Rev Psychiatry.* 2015;23(2):63–75.
5. Dunn KE, Brooner RK, Clark MR. Severity and interference of chronic pain in methadone-maintained outpatients. *Pain Med.* 2014;15(9):1540–1548.
6. Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: Effect of long-acting maintenance agent. *Drug Alcohol Depend.* 2001;63(2):139–146.
7. Doverty M, Somogyi AA, White JM, et al. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. *Pain.* 2001;93(2):155–163.
8. Wachholtz A, Gonzalez G. Co-morbid pain and opioid addiction: long term effect of opioid maintenance on acute pain. *Drug Alcohol Depend.* 2014;145:143–149.
9. Dunn KE, Finan PH, Andrew Tompkins D, Strain EC. Frequency and correlates of sleep disturbance in methadone and buprenorphine-maintained patients. *Addict Behav.* 2018;76:8–14.
10. Peles E, Schreiber S, Adelson M. Variables associated with perceived sleep disorders in methadone maintenance treatment (MMT) patients. *Drug Alcohol Depend.* 2006;82(2):103–110.
11. Stein MD, Herman DS, Bishop S, et al. Sleep disturbances among methadone maintained patients. *J Subst Abuse Treat.* 2004;26(3):175–180.
12. Sweeney MM, Antoine DG, Nanda L, et al. Increases in body mass index and cardiovascular risk factors during methadone maintenance treatment. *J Opioid Manag.* 2019;15(5):367–374.
13. Peles E, Schreiber S, Sason A, Adelson M. Risk factors for weight gain during methadone maintenance treatment. *Subst Abus.* 2016;37(4):613–618.
14. Brower KJ, Perron BE. Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. *Med Hypotheses.* 2010;74(5):928–933.
15. Ghitza UE. Overlapping mechanisms of stress-induced relapse to opioid use disorder and chronic pain: clinical implications. *Front Psychiatry.* 2016;7:80.
16. Lydon-Staley DM, Cleveland HH, Huhn AS, et al. Daily sleep quality affects drug craving, partially through indirect associations with positive affect, in patients in treatment for nonmedical use of prescription drugs. *Addict Behav.* 2017;65:275–282.
17. Smith MA, Lynch WJ. Exercise as a potential treatment for drug abuse: evidence from preclinical studies. *Front Psychiatry.* 2012;2:82.
18. Hosseini M, Alaei HA, Naderi A, Sharifi MR, Zahed R. Treadmill exercise reduces self-administration of morphine in male rats. *Pathophysiology.* 2009;16(1):3–7.
19. Smith MA, Pitts EG. Wheel running decreases the positive reinforcing effects of heroin. *Pharmacol Rep.* 2012;64(4):960–964.
20. Alizadeh M, Zahedi-Khorasani M, Miladi-Gorji H. Treadmill exercise attenuates the severity of physical dependence, anxiety, depressive-like behavior and voluntary morphine consumption in morphine withdrawn rats receiving methadone maintenance treatment. *Neurosci Lett.* 2018;681:73–77.
21. Abrantes AM, Blevins CE. Exercise in the context of substance use treatment: key issues and future directions. *Curr Opin Psychol.* 2019;30:103–108.
22. Wang D, Wang Y, Wang Y, Li R, Zhou C. Impact of physical exercise on substance use disorders: a meta-analysis. *PLoS One.* 2014;9(10):e110728. doi:10.1371/journal.pone.0110728.
23. Weinstock J, Wadeson HK, Vanheest JL. Exercise as an adjunct treatment for opiate agonist treatment: review of the current research and implementation strategies. *Subst Abus.* 2012;33(4):350–360.
24. Naugle KM, Fillingim RB, Riley JL. A meta-analytic review of the hypoalgesic effects of exercise. *J Pain.* 2012;13(12):1139–1150.
25. Dolezal BA, Neufeld EV, Boland DM, Martin JL, Cooper CB. Interrelationship between Sleep and Exercise: a systematic review. *Adv Prev Med.* 2017;2017:1–14.
26. Youngstedt SD, O'Connor PJ, Dishman RK. The effects of acute exercise on sleep: a quantitative synthesis. *Sleep.* 1997;20(3):203–214.
27. Centers for Disease Control and Prevention. Physical activity for a healthy weight. Healthy weight. 2015. https://www.cdc.gov/healthyweight/physical_activity/index.html. Accessed October 10, 2019.
28. Beitel M, Stults-Kolehmainen M, Cutter CJ, et al. Physical activity, psychiatric distress, and interest in exercise group participation among individuals seeking methadone maintenance treatment with and without chronic pain. *Am J Addict.* 2016;25(2):125–131.
29. Barry DT, Beitel M, Breuer T, et al. Conventional and unconventional treatments for stress among methadone-maintained patients: treatment willingness and perceived efficacy. *Am J Addict.* 2011;20(2):137–142.
30. Caviness CM, Bird JL, Anderson BJ, Abrantes AM, Stein MD. Minimum recommended physical activity, and perceived barriers and benefits of exercise in methadone maintained persons. *J Subst Abuse Treat.* 2013;44(4):457–462.
31. Muller AE, Skurtveit S, Clausen T. Many correlates of poor quality of life among substance users entering treatment are not addiction-specific. *Health Qual Life Outcomes.* 2016;14(1):39.
32. Stein MD, Caviness CM, Anderson BJ, Abrantes A. Sitting time, but not level of physical activity, is associated with depression in methadone-maintained smokers. *Ment Health Phys Act.* 2013;6(1):43–48.
33. Weiss L, Gass J, Egan JE, Ompad DC, Trezza C, Vlahov D. Understanding prolonged cessation from heroin use: findings from a community-based sample. *J Psychoactive Drugs.* 2014;46(2):123–132.
34. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.
35. Colledge F, Vogel M, Dürsteler-Macfarland K, et al. A pilot randomized trial of exercise as adjunct therapy in a heroin-assisted treatment setting. *J Subst Abuse Treat.* 2017;76:49–57.
36. Staub L, Gerber M, Vogel M, et al. How to develop and implement an exercise programme in a heroin-assisted treatment setting. *Heroin Addict Relat Clin Probl.* 2018;20(3):41–49.
37. Cutter CJ, Schottenfeld RS, Moore BA, et al. A pilot trial of a videogame-based exercise program for methadone maintained patients. *J Subst Abuse Treat.* 2014;47(4):299–305.
38. Pérez-Moreno F, Cámara-Sánchez M, Tremblay JF, Riera-Rubio VJ, Gil-Paisán L, Lucia A. Benefits of exercise training in Spanish prison inmates. *Int J Sports Med.* 2007;28(12):1046–1052.
39. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine Position Stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011;43(7):1334–1359.
40. Flack KD, Johnson LA, Roemmich JN. The reinforcing value and liking of resistance training and aerobic exercise as predictors of adult's physical activity. *Physiol Behav.* 2017;179:284–289.
41. Thiebaud RS, Funk MD, Patton JC, et al. Validity of wrist-worn consumer products to measure heart rate and energy expenditure. *Digit Heal.* 2018;4:1–7.
42. Jake-Schoffman DE, Silfee VJ, Sreedhara M, et al. Reporting of physical activity device measurement and analysis protocols in lifestyle interventions [published online July 17, 2019]. *Am J Lifestyle Med.* doi:10.1177/1559827619862179.
43. Kurti AN, Dallery J. Effects of exercise on craving and cigarette smoking in the human laboratory. *Addict Behav.* 2014;39(6):1131–1137.
44. Taylor AH, Oh H, Cullen S. Acute effect of exercise on alcohol urges and attentional bias towards alcohol related images in high alcohol consumers. *Ment Health Phys Act.* 2013;6(3):220–226.
45. Daniel JZ, Cropley M, Ussher M, West R. Acute effects of a short bout of moderate versus light intensity exercise versus inactivity on tobacco withdrawal symptoms in sedentary smokers. *Psychopharmacology (Berl).* 2004;174(3):320–326.