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Exercise as a Sex-Specific Treatment for Substance Use Disorder

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Abstract

Purpose of Review—Exercise is a promising treatment for substance use disorder that may reduce withdrawal symptoms and prevent relapse. In this review, we discuss recent evidence from clinical and preclinical studies for its efficacy, from a behavioral to a molecular level, in order to understand the exercise conditions that lead to beneficial effects. We also highlight the few recent findings of sex-specific differences.

Recent Findings—Clinical and preclinical findings show that exercise decreases withdrawal symptoms, including craving, in both males and females. Evidence from clinical studies support the efficacy of exercise to prevent relapse to smoking, although further research is needed to examine sex differences, establish long-term efficacy, and to determine if effects extend to other substance use disorders. Preclinical findings also support the potential utility of exercise to prevent relapse with evidence suggesting that its efficacy is enhanced in males, and mediated by blocking drug-induced adaptations that occur during early abstinence.

Summary—Sex differences and timing of exercise availability during abstinence should be considered in future studies examining exercise as an intervention for relapse. A better understanding of the neurobiological mechanisms underlying the efficacy of exercise to reduce

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Compliance with Ethics Guidelines

Conflict of Interest

Wendy J. Lynch, Jean Abel, Andrea M. Robinson, and Mark A. Smith declare they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

withdrawal symptoms and prevent relapse is needed to guide its development as a sex-specific treatment.

Keywords

addiction; animal models; biological mechanisms; clinical; drug-craving; drug-seeking; exercise; gender differences; gonadal hormones; intervention; neurobiology; physical activity; preclinical; relapse; sex differences; sex-specific; substance use disorder; treatment

Introduction

Exercise has been proposed as a treatment for substance use disorder that may reduce withdrawal symptoms and prevent relapse (1–3). The weight control benefits of exercise may be particularly attractive to women since they are more likely than men to report weight concerns as a contributor to relapse (4–5). The ability of exercise to decrease anxiety and withdrawal symptoms may also be particularly beneficial for women since they experience greater negative affect during withdrawal, and are more likely to attribute relapse to negative affect as compared to men (6–11).

Considerable evidence supports the potential for exercise to serve as a treatment for substance use disorder (1,3). Most of the recent evidence in this regard has been provided by studies conducted in men and women with tobacco and other substance use disorders showing that exercise reduces withdrawal symptoms including craving and negative affect (7–9,12–20). Studies in male and female smokers further suggest the potential for exercise to prevent relapse and improve treatment outcomes when combined with other smoking cessation treatments (21–25). Although few controlled trials have been conducted on exercise as a relapse intervention for other drugs of abuse, several recent pilot studies conducted in individuals, mostly men, undergoing treatment for substance use disorder demonstrate its feasibility and potential efficacy (26–33). Similar findings have been reported in male and female laboratory animals with results showing that exercise during abstinence, such as voluntary running in a wheel or forced running on a treadmill, reduces drug withdrawal signs (34–40), including craving (41–43), and prevents the development of incubation of drug-craving (44–52), an animal model of relapse defined by a progressive increase in drug-craving over abstinence (53). Exercise has also been suggested as a sex-specific prevention for substance use disorder, and evidence for these effects was reviewed in Part I (54; also see 55).

The efficacy of exercise, however, can be variable, particularly for relapse prevention (24–29, 56–59). While lack of power and compliance issues undoubtedly contribute to the variability (24–29,56–59), results from animal studies also demonstrate that certain exercise conditions may not be effective, and some may even increase relapse vulnerability (44,49). The ability of exercise to reduce or enhance withdrawal symptoms/craving and relapse vulnerability is likely determined by the underlying neurobiology which can vary between males and females, exercise conditions, drugs of abuse, and early versus later abstinence time-points (2). In this review, we will discuss recent evidence (2012–2017) from clinical and preclinical studies for the efficacy of exercise as a treatment for substance use disorder, from a behavioral to a molecular level, in order to understand the exercise conditions that

induce beneficial effects. We also highlight the few recent findings for sex-specific differences.

Overview of Clinical Findings

Most of the previous clinical work on exercise as a treatment for substance use disorder focused on effects on withdrawal symptoms/craving and smoking cessation in smokers (7–8). Recent work has expanded this investigation to include withdrawal symptoms/craving for other drugs of abuse (9,18–20), and feasibility for relapse prevention for other substance use disorders (21–33).

Withdrawal symptoms/craving in women and men

Numerous recent studies conducted in male and female smokers have demonstrated that exercise during abstinence reduces craving, anxiety, and negative affect and increases positive mood (Table 1; 12–17; for meta-analysis see 8). Similar effects of exercise have been reported in numerous recent studies conducted in men and women with other substance use disorders (18–20; for meta-analyses see 9,58). For example, acute aerobic exercise (cycling) decreased drug-craving in women and men undergoing residential treatment for methamphetamine use disorder (19), and chronic aerobic exercise (8-week treadmill interval training) decreased measures of depression in men and women undergoing residential treatment for an illicit substance use disorder (i.e., heroin, amphetamine, cannabis; 18). Recent studies have also shown that aerobic exercise during abstinence can offset deficits in inhibitory control (19–20) that have been linked to relapse (60).

These beneficial effects of exercise have been observed in a variety of settings, including laboratory, residential and out-patient treatment settings, for low, moderate and high intensity exercise, and for numerous types of exercise including aerobic, resistance/strength training, and mind-body such as yoga, as well as combined programs that include two or more of each exercise type (Table 1). Indeed, results from a recent meta-analysis showed that aerobic and mind-body exercise produced similar effects on withdrawal symptoms, drug-craving, and depression (9). While higher intensity exercise may induce greater effects (20,26), even light intensity exercise, such as walking, can induce beneficial effects (14–16,20,26). Indeed, preliminary findings show that both walking and jogging decrease craving in women and men with concurrent cocaine and tobacco-use disorder although effects did not reach statistical significance in this pilot study (26). The effects of exercise do appear, however, to depend on the substance used with results suggesting that its efficacy at reducing withdrawal symptoms and negative affect is more pronounced for illicit drugs as compared to nicotine and alcohol (8–9,58).

Sex Differences

Few studies have examined sex differences in the effects of exercise on drug withdrawal symptoms/craving. This is surprising considering that sex differences are recognized both for withdrawal symptoms in individuals with substance use disorder (e.g., 61–62), and for effects of exercise on negative affect in general populations of women and men (63–64). Of the few recent studies that have considered sex differences (12–13,17), and only one study

reported sex-specific analyses (13). This study was conducted in temporarily abstinent smokers, and showed that in women, but not men, acute exercise decreased anticipated relief from negative affect; whereas, in men, but not women, it decreased intention to smoke (13). While these results demonstrate that exercise decreases withdrawal symptoms in both men and women, they suggest that effects on certain withdrawal symptoms differ between men and women. Future studies using larger samples are needed to address this possibility, and to determine if there are sex differences in the effects of exercise on withdrawal symptoms/craving with other drugs of abuse.

Relapse Prevention in women and men

Evidence also indicates that exercise can benefit women and men with substance use disorders with regard to relapse prevention (Table 1). Most of this evidence is from smokers, with results showing that exercise increases abstinence to a level comparable to that observed with other smoking cessation treatments, and improves smoking-related outcomes when used as an adjunct to other treatments; for review see 65). For example, in females, an 8-week yoga intervention as an adjunct to cognitive-behavioral therapy produced a greater increase in abstinence as compared to cognitive-behavioral therapy plus a wellness intervention (21). Similar findings have been reported in men and women following aerobic exercise interventions (22–23). However, these effects appear to be more variable as compared those observed on withdrawal symptoms/craving (8). There are also individual differences in the efficacy of exercise as a smoking cessation aid with evidence for enhanced efficacy in some individuals (e.g., women with moderate-to-severe depression; 22 also see 25), but not apparent in others (individuals with low anxiety sensitivity; 23; pregnant woman; 56). Its long-term efficacy also remains controversial with results from a systematic review revealing significant long-term improvement in only 2 of 20 trials (at the 3 month follow-up; 57; also see 21–22,24–25,56). However, the majority of these studies are insufficiently powered for detecting long-term effects, and in many studies, exercise adherence is low/not verified and/or levels of exercise are not different from controls (e.g. 21–22,24–25,56). Future studies using larger sample sizes and sufficient/verifiable exercise interventions are needed to determine its long-term efficacy in men and women.

Although few randomized controlled trials have investigated exercise as a treatment for other substance use disorders, results from recent trials and pilot studies demonstrate its feasibility (26–33,59). For example, 4-weeks of aerobic exercise improved basic fitness in men and women with concurrent cocaine and tobacco-use disorder (26), and 8-weeks of endurance/resistance-exercise improved fitness in individuals, mostly men, undergoing residential treatment for methamphetamine use disorder (30). These studies have also demonstrated that exercise-based interventions are well-received and feasible within residential- and outpatient-treatment settings (27–33,59), and result in physiological changes that may enhance recovery (26,29–33).

Recent findings also provide preliminary support for the efficacy of exercise as a relapse intervention for substance use disorder (26,29,32–33,59). For example, women and men who completed a 10-week group exercise program during residential treatment were less likely than non-completers to report drug use at the end of the program (33). Similarly, an 8-

week aerobic/resistance exercise intervention decreased drug use in women and men undergoing residential treatment for methamphetamine use disorder; however, this decrease was only significant in compliant individuals (attended 16 of 24 sessions, or an average of 2 sessions/week), or in individuals with a less severe methamphetamine use disorder (29). Several recent pilot studies have also reported non-significant trends, variable effects of exercise, or a lack of long-term efficacy (26,29,32,59) indicating that, like its efficacy as a smoking cessation aid, its efficacy to prevent relapse may be relatively modest. However, the majority of this work is based on small pilot studies; larger randomized controlled trials are needed to fully evaluate its efficacy. Compliance issues have also been noted in many trials with exercise (27–29,32); several methods are now being incorporated to improve exercise adherence (e.g. contingency management, cooperative dialog prior to randomization; 66–67). The use of such procedures may be critical particularly considering that exercise, though feasible and well-received by a majority of individuals, may be a “hard-sell” for individuals who have traditionally neglected exercise because of time, money, or health-related concerns.

Sex Differences

Results from the few recent studies that have examined sex differences in the feasibility and efficacy of exercise to prevent relapse have revealed conflicting results. For example, higher retention and greater efficacy were reported in men versus women in smoking cessation studies (24,57); whereas higher retention was observed in women versus men in studies of exercise for treating alcohol use disorder (58). It is notable that similar sex differences are also reported for outcomes among smokers versus alcohol/illicit drug users following traditional treatment. Women are less successful at maintaining smoking abstinence than are men (68); whereas, they do just as well, if not better, than men during treatment for alcohol and illicit drug use disorder (11). Thus, it is possible that sex differences in general treatment outcomes contribute to differences observed following exercise. It is also notable that research on exercise has focused preferentially on females for smoking cessation (e.g. 21–22,25,56); whereas, males tend to be over-represented in studies on illicit drugs and alcohol (e.g. 30–31,33,58). Future studies are needed to address sex differences using larger samples.

Overview of Preclinical Findings

As with findings in humans, recent findings in animals indicate that exercise can decrease drug withdrawal severity/craving and relapse vulnerability as assessed following extended access drug self-administration and protracted abstinence (Table 2).

Withdrawal severity/craving in female and male laboratory animals

Recent findings show that voluntary wheel running during alcohol withdrawal protects against seizures in male and female rats (34–35) indicating that exercise reduces drug withdrawal severity in both sexes. Voluntary or forced running during morphine withdrawal decreases physiological and behavioral signs of withdrawal (i.e., thermal sensitivity, wet dog shakes), and offsets withdrawal-induced anxiety and cognitive deficits in males (36–38).

Similar results have been observed for the effects of forced swimming during morphine and methamphetamine withdrawal in males (39–40).

Concurrent and contemporaneous (before and after sessions) wheel running also decreases drug-craving during withdrawal (41–43). In these studies, craving is determined by measuring drug-seeking (i.e., lever pressing) under extinction conditions (drug is not available), and in response to various stimuli that reinstate responding (e.g., small drug doses/primes, drug-associated cues, stress). This work has focused on cocaine-craving, with results demonstrating that the effects of wheel running depend on the cues used to trigger craving. For example, while wheel running consistently decreases cue-induced craving in both males and females (41–43), its efficacy at reducing cocaine-primed craving is variable between the sexes (41–43) suggesting that drug-primed craving may be more difficult to modulate with exercise. Notably, recent findings show that this variability can be reduced by combining exercise with pharmacological approaches. For example, combining wheel running with progesterone, a hormone-based medication that has shown promise for treating substance use disorder in humans (69), effectively reduced craving in both males and females, and in males, produced a greater reduction in craving as compared to either treatment alone (42). Similar effects have also been observed in females, where pretreatment with atomoxetine, a medication that has shown promise for treating stimulant use disorder in humans (69), improved the efficacy of exercise at reducing cocaine-primed craving (43). These findings suggest that combined exercise-pharmacological approaches can augment/broaden the efficacy of exercise to include a range of craving-triggers in both sexes.

Sex Differences

Several recent studies have compared the effects of wheel running on drug withdrawal/craving between males and females with mixed results (34,41–42). For example, wheel running during alcohol withdrawal similarly reduced seizures in males and females (34), and wheel running during cocaine withdrawal prior to reinstatement testing similarly reduced cue-induced and cocaine-primed craving in males and females (41). In contrast, while concurrent wheel running similarly reduced stress- and cue-induced cocaine-craving in females and males, it decreased cocaine-primed craving in females, but not males (42). Although these findings indicate that the efficacy of exercise at reducing drug withdrawal/craving are either comparable or more pronounced in females versus males, they are tempered by the fact that females run at higher levels as compared to males (34,41–42). Thus, further studies controlling for levels of running are needed to determine the relative efficacy of exercise between males and females.

Relapse Vulnerability in female and male laboratory animals

Recent studies also demonstrate that voluntary wheel running during abstinence attenuates the incubation of drug-craving (Table 2). This anti-relapse effect of exercise has been observed in males and females, adolescent and adult-onset models, for multiple drugs of abuse (cocaine, nicotine, methamphetamine), and for cue-, context-, and drug-induced craving, but not stress-induced craving (44–52). Although levels of running do not consistently predict effects on the incubation of craving (64–65), effects become more

pronounced with increasing exercise access such that high access (6-hr/day) blocks the incubation effect (46–47). Forced exercise at low-to-moderate levels also attenuate the incubation effect in response to cues and drug-primes; however, high levels of forced exercise increase drug-primed craving (49). These findings indicate that the efficacy of exercise at reducing drug-craving depend on the stimuli present in the environment and indicate the potential for forced exercise to increase craving.

The timing of exercise availability during abstinence also appears to be critical for inducing protective effects (44). For example, results in male rats showed that wheel running beginning during early abstinence (days 1–7) robustly decreased subsequent cocaine-craving (day 15), whereas exercise beginning later during abstinence (days 8–14), was not effective, and in some cases, increased craving (44). These findings are striking given that the time from the last exercise session to reinstatement testing was much longer in the early exercise group, and suggests that if exercise is properly timed during abstinence, it can provide enduring protection against relapse. These findings also suggest that exercise should be introduced early in the course of treatment. This point is critical given that most of the trials conducted with exercise, with the exception of smoking cessation studies, introduce exercise well after initiation of abstinence.

Sex Differences

Both of the recent studies that examined the effects of exercise on relapse vulnerability in males and females observed sex differences (47,51), with evidence suggesting that efficacy is enhanced in males and dependent on hormonal status in females. For example, while modest wheel running (2-hr/day) during abstinence decreased the incubation of cocaine-craving in males, its efficacy in females depended on whether they were tested during estrus, when craving is high, or during non-estrus phases, when levels of craving are lower (47). Specifically, modest wheel running during abstinence similarly decreased the incubation of cocaine-craving in males and in females tested during non-estrus phases, but had no effect in females tested during estrus. Females tested during estrus did show decreases in the incubation of cocaine-craving, but only following high wheel access conditions (6-hr/day; 47) suggesting that the efficacy of exercise, particularly at modest levels, can be negated during periods of high craving.

Recent results also show that in females, but not males, access to a locked wheel also prevented the incubation of cocaine and nicotine-craving (47,51), indicating that the presence of the wheel is sufficient to reduce craving in females. These results parallel findings from a community intervention study showing that while exercise-based enrichment programs decreased smoking in both boys and girls, only girls benefitted from non-exercise based enrichment programs (70).

Neurobiological Mechanisms

The mechanisms underlying the efficacy of exercise as a treatment for substance use disorder are likely mediated, at least in part, via interactions with dopamine in the reward pathway. Voluntary wheel running activates the same mesolimbic reward pathway as drugs

of abuse consisting of dopaminergic projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex (71–73) with recent evidence showing that running induces excitatory dopaminergic signaling in the nucleus accumbens (74). These findings are important because they suggest that exercise may be able to offset the hypofunctioning that occurs in the mesolimbic system following chronic drug exposure (75). Exercise can also protect against drug-induced toxicity, which may underlie enhanced withdrawal and craving as well as cognitive deficits (76–77). For example, wheel running prevented methamphetamine-induced depletion of dopamine and serotonin transporters in striatal regions of male rats (77).

Exercise may also reverse drug-induced neuroadaptations associated with withdrawal symptoms/craving and relapse vulnerability. For example, recent findings in humans show that modest levels of aerobic exercise during treatment reversed methamphetamine-induced deficits in striatal D2/D3 receptors (78). This finding is significant considering that deficits in D2/D3 receptors can persist even after months/years of abstinence, and are believed to underlie vulnerability to relapse in both men and women (79). Wheel running during abstinence also blocked the incubation of methamphetamine-craving and normalized associated increases in periaqueductal gray dopamine neurons (52), which project to the VTA (80). Glutamatergic signaling in the reward pathway is another likely candidate given strong evidence implicating AMPA receptors in the incubation effect (81). While few studies have examined this possibility in addiction models, results from findings in males using models of Parkinson's Disease, which is also characterized by hyper-excitability/abnormal glutamatergic drive, show that moderate levels of forced running reduce hyper-excitability (upregulation of GluA2/3, and downregulation of GluA1 receptors) in cortical and striatal regions (e.g., 82).

Exercise also affects epigenetic mechanisms that may offset withdrawal symptoms/craving and provide long-term protection against relapse. Both exercise and drugs of abuse modify chromatin containing the brain-derived neurotrophic factor (BDNF) gene (83–85). The efficacy of exercise at reducing anxiety and depression is believed to be mediated via Bdnf signaling (6). Bdnf is also one of the few markers that is positively associated with relapse vulnerability in humans (86) and the incubation effect in animals (87). Specifically, drug-craving and markers of Bdnf signaling in the reward pathway are low during early abstinence, but as abstinence continues, both craving and markers of Bdnf signaling increase (87). Notably, the incubation of craving and associated increase in Bdnf signaling can be prevented by upregulating Bdnf during early, but not late, abstinence (88). Given that exercise also upregulates Bdnf (85,89), it's possible that its ability to block the incubation of drug-craving may occur via upregulation of Bdnf during early abstinence. In support of this idea, wheel running beginning during early abstinence dose-dependently reduced the incubation of cocaine-craving and Bdnf exon IV expression, a marker of epigenetic regulation, in the prefrontal cortex (46). Additionally, exercise beginning during late abstinence, which would be expected to amplify Bdnf signaling, was not effective, and in some cases, increased craving (44). These findings provide strong support for Bdnf signaling as a mechanism underlying the efficacy of exercise to prevent relapse although further research is needed to determine if they extend to other drugs of abuse and to females. These findings may also help explain findings from other studies where exercise increased craving/

reward (49,91), and suggest that even modest exercise has the potential to amplify signaling pathways that promote relapse. It is important to note that exercise initiated at later points during abstinence could still be effective; however, these effects would likely rely on exercise's ability to acutely reduce craving, possibly through interactions with dopamine.

Sex Differences

Most of the work conducted on the neurobiology of exercise has been conducted in males, and very few studies have compared males and females. Given instances of sex differences in the efficacy of exercise at reducing withdrawal/craving and relapse vulnerability (42,47), the underlying neurobiology is also likely to differ. For example, evidence indicates that females have an increased sensitivity to rewarding stimuli and an enhanced dopaminergic response to drugs of abuse and natural rewards (92); thus, it is possible that the enhanced sensitivity to the effects of concurrent exercise on drug-craving observed in females (42), is mediated via dopaminergic signaling. Females also run at higher levels than males (34,41–42), which may also produce greater activation of mesolimbic dopamine.

Recent work also indicates an enhanced sensitivity in males to the effects of exercise on the incubation of craving (47). This effect of exercise may occur via epigenetic changes that counter drug-induced adaptations (46), suggesting that in males, less exercise is needed to block drug-induced adaptations. In support of this idea, exercise induces a greater increase in Bdnf in men versus women (serum/plasma; 93), and in male versus female animals (hippocampal Bdnf exon IV expression; 94). However, the occurrence of sex differences in the effects of exercise on Bdnf differs following forced versus voluntary exercise (95) and may differ between brain regions. Future research is needed to determine the role of Bdnf signaling as a mechanism for sex differences in the efficacy of exercise as an intervention for substance use disorder. Future research should also expand the investigation of sex differences to other signaling pathways (e.g., glutamate, opioid, endocannabinoid, serotonin) and to other drugs of abuse.

Conclusions and Future Directions

Results from both human and animal studies show that exercise during abstinence decreases withdrawal symptoms, including craving. While these effects have been observed in both males and females, little is known regarding potential sex differences. Further research is necessary to address this question considering that withdrawal symptoms differ between males and females (61–62), and may contribute to sex differences in relapse vulnerability (5,10–11). The efficacy of exercise as an intervention for substance use disorder also has not yet been examined as a function of hormonal status in women. This may be critical given the preclinical findings showing that the efficacy of exercise is dependent upon hormonal status at the time of testing (47,51), and given findings in women showing that withdrawal symptoms and treatment outcome can vary with menstrual cycle phase (96).

Evidence from men and women also supports the use of exercise as a smoking cessation aid, although further work is needed to establish its long-term efficacy and determine sex differences. Results in men and women with other substance use disorders demonstrate that

exercise is a well-tolerated intervention that can be used even during periods of initial recovery when withdrawal symptoms are high. This is important given preclinical findings demonstrating that the efficacy of exercise is most pronounced if it's initiated during early abstinence (44). Although power and compliance issues in human studies may underlie some of the variability observed for the efficacy for exercise as a relapse prevention, preclinical results suggest that the exercise conditions used may also contribute. For example, high-levels of forced running during abstinence (49), and moderate-levels of voluntary running during late abstinence (44), increased drug-craving suggesting that exercise needs to begin during early abstinence and/or maintained throughout abstinence to be effective. Findings from male and female animals also support the efficacy of exercise for reducing relapse vulnerability for other drugs of abuse, with effects vary between males and females and early versus late abstinence.

Recent findings from clinical and preclinical studies indicate that exercise can be combined with other interventions to enhance and broaden its efficacy (42–43). There are few contraindications for exercise; it can be combined with most behavioral, environmental, and pharmacological interventions that are commonly used in treating substance use disorder. Indeed, recent clinical data show that exercise can be easily integrated into comprehensive treatment programs (1,30). One possibility would be to combine exercise beginning during early abstinence with a medication or other environmental interventions that also enhance Bdnf signaling. This type of approach may be particularly beneficial for women given that exercise is expected to produce less of an increase in Bdnf in women versus men (93). Future studies should also examine exercise in the context of contingency management for substance use disorders, such that exercise is also reinforced to promote long-term abstinence.

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Table 1

Clinical Studies: Effects of Exercise on Withdrawal Symptoms/Craving and Feasibility/Efficacy for relapse Prevention

Withdrawal Symptoms/Craving				
1st author (ref)	Substance Use Disorder/Subjects (% women)	Exercise Schedule	Study Design	Effect of exercise Sex differences/sex-specific effects
Abrantes (12)	<u>Tobacco</u> : Sedentary men and women in a smoking cessation study (N=61; 65.5%; USA).	12-week group aerobic exercise (1, 15–40-min session/week) + exercise prescription (2–4 days/week).	Randomized controlled trial (RCT) comparing standard smoking cessation treatment plus exercise or health education (control) on mood, anxiety, and craving prior to and following the quit attempt.	-77.5% session completion. -Decreased anxiety, but did not affect smoking, prior to quit attempt. -Decreased craving and anxiety and increased positive mood during abstinence. -Controlled for sex; no information on sex-specific differences.
Allen (13)	<u>Tobacco</u> : Abstinent men and women smokers (N=38; 60.5%; USA).	Acute aerobic exercise (6–12 min; cycling).	Sex-specific (secondary) analysis of the effects of exercise on withdrawal symptoms (craving, urge and intention to smoke, anticipated relief from negative affect) during a self-initiated quit attempt.	-Decreased all measures of withdrawal symptoms. -In women, but not men, decreased anticipated relief from negative affect. -In men, but not women, decreased intention to smoke.
Fong (14)	<u>Tobacco</u> : Abstinent men and women smokers (N=26; 54%; Canada).	An acute bout of light-moderate intensity aerobic exercise (15-min; treadmill walking)	Randomized pilot comparing exercise versus sitting (control) on stress-induced withdrawal symptoms, craving, and <i>ad libitum</i> smoking.	-Decreased stress-induced withdrawal symptoms and craving. -Did not affect smoking. -No analysis of sex differences.
Janse Van Rensburg (15)	<u>Tobacco</u> : Abstinent men and women smokers (N=162; 34%; USA).	Acute aerobic exercise (30 min; treadmill) at a light or high intensity (40 versus 75% of heart rate reserve, HRR).	RCT comparing light versus high intensity exercise or passive (control) on craving, mood, and reactivity to smoking cues before and immediately after session and cues.	-Both light and vigorous exercise decreased craving and increased positive affect. -Vigorous exercise decreased reactivity to cues. -Not powered to assess sex differences.
Prapavessis (16)	<u>Tobacco</u> : Abstinent sedentary pregnant smokers (N=32; England and Canada)	An acute bout of mild-to-moderate intensity exercise (20 min; walking on treadmill).	Randomized pilot comparing the effects of exercise versus sitting (control) on craving and withdrawal symptoms immediately before, during, immediately and 10, 20, and 30 min after the session.	-Reduced pre-session craving at all time-points. -Non-significantly decreased withdrawal symptoms.
Tritter (17)	<u>Tobacco</u> : Women and men in a smoking cessation study (N=30; 67%; USA).	An acute bout of moderate-intensity aerobic exercise (20-min; treadmill walking/jogging).	Randomized pilot comparing acute NRT (lozenge) with or without (control) exercise on craving during abstinence.	-Further enhanced the decrease in craving -No sex differences at baseline; no information regarding sex-specific effects of exercise.
Haasova (8)	<u>Tobacco</u> : Abstinent men and women smokers (19 studies).	1-day to 52-week exercise interventions (aerobic, mind body; various intensities).	Meta-analysis examining the effects of acute exercise or sitting (control) on desire to smoke during abstinence.	-Consistently reduced in craving. -No analysis of sex differences.
Flemmen (18)	<u>Illicit</u> : Women and men in residential treatment (N=24; 29%; USA).	8-week treadmill interval training (4 × 4 minutes at 90–95% of HRR; 3 sessions/week).	Randomized pilot comparing standard residential treatment with or without (control) exercise on fitness and mood (depression, anxiety).	-75% group retention. -Improved cardiorespiratory fitness. -Decreased measures of depression. -No analysis of sex differences.

Withdrawal Symptoms/Craving				
1 st author (ref)	Substance Use Disorder/Subjects (% women)	Exercise Schedule	Study Design	Effect of exercise Sex differences/sex-specific effects
Wang (19)	<u>METH</u> : Women and men in a police-ordered treatment program (N=24; 20%; China).	Acute aerobic exercise (30-min; cycling at moderate intensity).	Randomized pilot comparing exercise versus reading (control) on craving and reaction time/response accuracy (Go/No-go task) before, during, immediately and 50-min after sessions.	-Decreased craving at each of the time-points as compared to pre-exercise ratings and control. -Facilitated inhibitory performance as compared to controls. -No analysis of sex differences.
Wang (20)	<u>METH</u> : Women and men in a police-ordered treatment program (N=92; 15%; China).	Acute aerobic exercise (30 min; cycling) at a light, moderate, or high intensity (40–50%, 65–75% or 85–95% HRR).	Randomized pilot comparing exercise versus reading (control) on craving and reaction time/response accuracy (Go/No-go task) before, during, immediately and 50-min after sessions.	-Greater intensity exercise produced greater decreases in craving. -Moderate exercise was associated with the fastest response times and highest response accuracy. -No analysis of sex differences.
Wang (9)	<u>Alcohol, Tobacco, and/or Illicit</u> : Women and men in a treatment or laboratory setting (22 studies).	10-days to 6-month exercise interventions (aerobic, mind body; various intensities).	Meta-analysis of RCTs comparing exercise versus control on withdrawal symptoms, anxiety, depression, and abstinence.	-Reduced withdrawal symptoms, anxiety, and depression. -Increased abstinence. -Largest effects for illicit drug use disorder. -Similar effects of aerobic versus mind-body -Both low and high intensity exercise is effective. -No analysis of sex differences.
Feasibility/Relapse Prevention				
Bock (21)	<u>Tobacco</u> : Sedentary women in a smoking cessation study (N=55; 100%; USA).	8-week group-based yoga program (2, 1-hr sessions/week).	Randomized pilot comparing cognitive-behavioral therapy plus yoga or wellness on smoking abstinence and anxiety at completion and after 3 and 6 months.	-76.2% exercise session attendance. -Increased smoking abstinence and decreased anxiety at study completion. -Effects at follow-up did not reach significance.
Patten (22)	<u>Tobacco</u> : Women with moderate to severe depressive symptoms in a smoking cessation study (N=30; 100%; USA).	12-week supervised vigorous aerobic exercise (3, ~30 min sessions/week, e.g., vigorous jogging, defined by HRR).	Randomized pilot to establish feasibility of standard smoking cessation treatment plus exercise or health education (control) on adherence and abstinence at study completion, and 6 months post-target quit.	-72% group adherence rate. -Greater abstinence at study completion compared to control (73 versus 33%). -No difference in abstinence at followup.
Smits (23)	<u>Tobacco</u> : Sedentary men and women with elevated anxiety in a smoking cessation study (N=136; 52%; USA).	15-week supervised vigorous aerobic exercise (3, 35 min sessions/week; treadmill jogging) beginning 5 weeks before the quit attempt.	RCT comparing standard smoking cessation treatment plus exercise or wellness education (control) on weekly and long-term abstinence 4 and 6 months after the quit attempt.	-Increased weekly and long-term abstinence. -Effective in individuals with high, but not low, anxiety sensitivity. -No analysis of sex differences.
Linke (24)	<u>Tobacco</u> : Sedentary men and women in a smoking cessation study (N=38; 60.5%; USA).	12-week exercise prescription beginning on the quit date (instructed to exercise each time craving occurred; ~15 min/bout; ~60 min/day; aerobic, strength, stretching).	Randomized pilot comparing an internet-based smoking cessation program with or without (control) exercise on smoking and levels of exercise (number and length of bouts).	-57.9% study completion. -Poor adherence (~1 bout/day; 33% of all days). -Daily cigarettes decreased in all groups. -Positive association between self-reported exercise and smoking reduction rates. -Higher retention in men (80% versus 48%).
Prapavessis (25)	<u>Tobacco</u> : Women in a smoking cessation study (N=413; Canada).	14-week group-to-home tapered aerobic exercise (e.g., 45-min jogging/ biking; weeks 1–8: 3	RCT comparing NRT for smoking cessation with exercise or equal-contact non-exercise (control) on	-Increased abstinence at each of the time-points, but only the difference at study completion

Withdrawal Symptoms/Craving				
1 st author (ref)	Substance Use Disorder/Subjects (% women)	Exercise Schedule	Study Design	Effect of exercise Sex differences/sex-specific effects
		session/week; weeks 9–14: 1 session/week plus exercise prescription (3, 45 min sessions/week at home)	continuous smoking abstinence from quit attempt to study completion and 3 and 10 months later.	approached significance (57 vs 43 %, p = 0.08).
Ussher (56)	Tobacco: Pregnant smokers (10–24 weeks) in a smoking cessation study (13 hospitals; N=785; England)	14 exercise sessions (supervised treadmill plus exercise consultations).	Parallel group, randomized trial of cognitive behavioral therapy for smoking cessation with and without (control) exercise on adherence and continuous abstinence from quit to end of pregnancy.	-No effect on abstinence. -Self-reported exercise increased over the course of the study, but accelerometer data indicated no between group differences in levels of exercise. -Fewer caesarean births.
Ussher (57)	Tobacco: Women and men in a smoking cessation study (20 studies; N=5,870)	~4–19 week exercise interventions (aerobic, mind body; various intensities)	Systematic review of RCTs on the long-term efficacy (3 months) of exercise alone or as an adjunct to other smoking cessation treatments.	-Only 2 of 20 trials show long-term efficacy. -Most studies were not sufficiently powered to detect long-term efficacy or didn't ensure adherence with a sufficiently intense intervention. -Of 4 trials that examined sex differences, 3 found no differences, and 1 found better efficacy in men.
De La Garza (26)	Cocaine and Tobacco: Women and men in a laboratory setting (N=24; 21%; USA).	4-week exercise intervention comparing treadmill walking versus jogging (3, 30 min sessions/ week).	Randomized pilot comparing exercise versus sitting (control) on cocaine and tobacco craving and use, and fitness.	-~90% group retention; 100% compliance. -Improved fitness. -Non-significant reductions in craving and self-reported and biochemically verified cocaine use. -Less robust effects for tobacco versus cocaine. -Walking and running produced similar effects. -Not powered to assess sex differences.
Colledge (27)	Heroin: Men and women in a heroin-assisted outpatient treatment program (N=24; 37.5%; Switzerland).	12-week exercise program (2 sessions/week; climbing, badminton, strength training, boxing, dance, and walking).	Randomized pilot comparing heroin-assisted treatment plus exercise or non-exercise (control) on compliance, substance use, and psychological/ physiological health.	-93% group retention. -92% compliance (attended 5 of 23 sessions). -Decreased substance use in both groups. -No effect on psychological/ physiological health. -No analysis of sex differences.
Cutter (28)	Heroin: Men and women in a methadone maintenance program (N=29; 59%; USA).	8-week Wii Fit exergame intervention (5, 20–25 min session/week; i.e., aerobic, strength, balance, yoga).	Randomized pilot comparing methadone maintenance plus exercise or sedentary game-play (control) on adherence/ retention, satisfaction, and illicit drug use.	-93% study completion; 65% session attendance. -High ratings of satisfaction. -Decreased substance use in both groups. -No analysis of sex differences.
Rawson (29)	METH: Women and men in residential treatment (N=135; 20%; USA).	8-week exercise intervention (3, 55 min sessions/week; treadmill plus weight training).	RCT comparing standard residential treatment plus exercise or health (control) on METH use at 1, 3, and 6 months post-treatment in compliant individuals (attended 16 of 24 sessions) and lower versus higher severity METH users.	-73% group adherence rate. -Non-significant decreases in METH. -Decreased METH use at each timepoint in compliant individuals, and in lower severity METH users. -Controlled for sex; no information on sex-specific differences.
Dolezal (30)	METH: Women and men in residential	8-week endurance/ resistance training program	Randomized pilot comparing standard	-74% group retention rate; >90% compliance.

Withdrawal Symptoms/Craving				
1 st author (ref)	Substance Use Disorder/Subjects (% women)	Exercise Schedule	Study Design	Effect of exercise Sex differences/sex-specific effects
	treatment (N=39; 10%; USA).	(3, 1-hr sessions/week; supervised jogging/running plus lifting)	residential treatment plus exercise or health education (control) on fitness.	-Improved cardiorespiratory fitness and strength. -Decreased body weight and body fat. -Predominantly a male sample.
Zhu (31)	<u>Stimulant</u> : Men in a police-ordered rehabilitation program for stimulate use disorder (N=60; China).	12-week Tai Chi exercise intervention.	Randomized pilot comparing standard treatment with or without exercise (control) on quality of life (physical health/fitness) at study completion.	-Increased levels of energy and physical health including balance.
Trivedi (32)	<u>Stimulant</u> : Women and men in residential treatment (9 facilities; N=302; 40%; USA).	12-week dosed, supervised walking intervention (3, 50-min sessions/week; 12 kcal/kg/week).	RCT comparing standard residential treatment plus exercise or health education on percent days abstinent.	-69% group completion rate; lower adherence in the exercise group (64% versus 75%). -Modest increase in abstinence after adjusting for adherence. -No significant interactions with sex.
Muller (33)	<u>Alcohol and/or Illicit</u> : Sedentary men and women in residential treatment (N=35; 26%; Norway).	10-week group exercise intervention (3, 30-min coach-led sessions/week; walking/running, ball games, strength training).	Non-random pilot comparing completers of exercise intervention versus non-completers (didn't attend any exercise sessions) on drug use, abstinence, quality of life, and mental distress before and after the intervention.	-69% group retention. -Improved quality of life, and decreased anxiety and depression. -Decreased substance use in both groups. -Completers were less likely to report drug use at the end of the program (26% versus 63%). -No analysis of sex differences.
Hallgren (58)	<u>Alcohol</u> : Women and men in a treatment or laboratory setting (19 studies).	1-day to 52-week exercise interventions (aerobic, mind body; various intensities).	Meta-analysis of randomized and non-randomized studies comparing exercise versus control on alcohol use and treatment and health outcomes.	-No effect on daily alcohol consumption. -Reduced measures of depression. -Improved physical fitness. -Higher completion rates in women versus men.
Hallgren (59)	<u>Alcohol</u> : Individuals in outpatient treatment (N=18; sex not provided; Sweden).	10-week group yoga program (1, 1.5-hr session/week).	Randomized pilot comparing standard outpatient treatment with or without (control) exercise on mood, quality of life, and alcohol consumption at 6-months.	-89% group retention rate. -Non-significant decrease in alcohol consumption. -No effect on measures of stress/anxiety. -Demographics, including sex, were not provided.

Table 2

Preclinical Studies: Effects of Exercise on Withdrawal Severity/Craving and Relapse Vulnerability

Withdrawal Severity/Craving				
1st author (ref)	Subjects	Exercise Schedule	Drug and Study Design	Effect of exercise Sex differences/sex-specific effects
Devaud (34)	Male and female rats	Unlimited voluntary wheel running or locked/no-wheel access throughout study.	<u>Alcohol</u> : seizure thresholds 1 or 3 days following alcohol liquid diet (14 days).	-Attenuated withdrawal-induced seizure susceptibility in both males and females. -Increased ethanol consumption in both sexes. -Females ran more than males.
McCulley (35)	Male rats	Unlimited voluntary wheel running or locked/no-wheel access throughout study.	<u>Alcohol</u> : seizure thresholds 1 or 3 days following alcohol liquid diet (14 days).	-Attenuated withdrawal-induced seizure susceptibility.
Balter (36)	Male mice	Unlimited voluntary wheel running or no-wheel access prior to and following morphine dependence.	<u>Morphine</u> : thermal sensitivity during withdrawal (spontaneous) in dependent mice (2 treatments/day, 5.5 days).	-Attenuated withdrawal-induced increases in thermal sensitivity.
Miladi-Gorji (37)	Male rats	Unlimited voluntary wheel running or no-wheel access during conditioning.	<u>Morphine</u> : anxiety (elevated plus maze, EPM), and withdrawal signs in dependent rats (2 treatments/day, 10 days).	-Decreased anxiety and withdrawal signs.
Mokhtari-Zaer (38)	Male rats	Unlimited voluntary wheel running or forced treadmill running (30-min/day) during withdrawal.	<u>Morphine</u> : cognitive deficits (EPM, inhibitory avoidance), and withdrawal signs in dependent rats (2 treatments/day, 10 days).	-Reduced withdrawal signs. -Enhanced cognitive functioning in controls. -Attenuated morphine-induced cognitive deficits. -Similar efficacy of voluntary versus forced exercise.
Fadaei (39)	Male rats	Forced swimming (5, 45-min sessions/week, 2 or 3 weeks) or no swimming during the development of dependence and withdrawal.	<u>Morphine</u> : withdrawal signs, anxiety (EPM), anhedonia (sucrose preference) and consumption following abstinence in dependent rats (2 treatments/day, 14 days).	-Decreased withdrawal signs, anxiety, and anhedonia. -Decreased consumption following abstinence.
Damghani (40)	Male rats	Forced swimming (5, 45-min session/week) or no swimming during withdrawal.	<u>Methamphetamine</u> (METH): anxiety (EPM), antidepressant effects (forced swim test) and consumption in dependent rats (2 treatments/day, 14 days).	-Produced anti-depressant and anxiolytic effects. -Decreased consumption following abstinence.
Smith (41)	Male and Female rats	Unlimited voluntary wheel running or no-wheel access prior to training (6 weeks) and prior to and following each session.	<u>Cocaine</u> : extinction, primed- and cue-induced craving (assessed using a between-session design after short access SA).	-Decreased extinction and cued and primed cocaine-craving in both males and females. -Females ran more than males; yet the effects of exercise were similar in males and females.
Zlebnik (42)	Male and female rats	Concurrent voluntary wheel running or locked-wheel access during extinction and cocaine-craving testing.	<u>Cocaine</u> : extinction (14 days) and cued, primed, stress, cued+stress, and cued+ primed craving (assessed after short access SA and extinction) with or without exercise and progesterone pretreatment.	-Decreased cued, stress, cued+stress, and cued+ primed craving in both males and females. -Decreased cocaine-craving during extinction and in response to primes in females, but not males.

Withdrawal Severity/Craving				
1 st author (ref)	Subjects	Exercise Schedule	Drug and Study Design	Effect of exercise Sex differences/sex-specific effects
				-Progesterone enhanced exercise's efficacy in males.
Zlebnik (43)	Female rats	Concurrent voluntary wheel running or locked-wheel access during the reinstatement test sessions.	<u>Cocaine</u> : cued and primed craving (assessed after short access SA and extinction) with or without atomoxetine pretreatment.	-Both treatments decreased cue-induced craving. -Only the combined treatment reduced cocaine-primed craving.
Relapse Vulnerability				
Beiter (44)	Male rats	Voluntary wheel running (2-hr/day) or locked-wheel access during early, late, or throughout abstinence (days 1–7, 8–14, or 1–14).	<u>Cocaine</u> : incubation of cue-induced craving (assessed using a within-session extinction/reinstatement procedure after extended access SA and 14 days of abstinence).	-Exercise beginning during early, but not late, abstinence decreased cocaine-craving (extinction and in response to cues).
Ogbonmwan (45)	Male rats	Unlimited voluntary wheel running or no-wheel access during abstinence with sessions continuing until either immediately or 24-hr before testing.	<u>Cocaine</u> : incubation of cue- and stress-induced craving (assessed using a within-session design after short access SA, extinction, and 3-weeks of abstinence).	-Blocked cue-induced increases in craving. -Did not affect stress-induced craving. -Acute exercise was not necessary to decrease craving.
Peterson (46)	Male rats	Voluntary wheel running (1, 2, or 6 hr/day) or locked-wheel access during abstinence.	<u>Cocaine</u> : incubation of cue-induced craving (assessed using a within-session extinction/reinstatement procedure after extended access SA and 14 days of abstinence).	-Dose (session-length)-dependently decreased cocaine-craving in response to cues.
Peterson (47)	Male and female rats	Voluntary wheel running (1, 2, 6, or 24-hr/day) or locked/no-wheel access during abstinence.	<u>Cocaine</u> : incubation of cue-induced craving (assessed using a within-session extinction/reinstatement procedure after extended access SA and 14 days of abstinence) in males and in females tested during estrus versus non-estrus phases.	-Dose-dependently decreased craving in both sexes. -Males ran less and showed a greater response to exercise as compared to females. -Locked wheel also decreased craving in females. -Extended wheel access was necessary to decrease estrus-heightened cocaine-craving in females.
Zlebnik (48)	Female rats	Unlimited voluntary wheel running or locked-wheel access during abstinence.	<u>Cocaine</u> : incubation of cue-induced craving (assessed using a within-session extinction/reinstatement procedure after extended access SA and 3 or 30 days of abstinence).	-Blocked incubation of cocaine-craving over abstinence.
Thanos(49)	Male rats	Forced running on a treadmill under low versus high conditions (1 versus 2 hr/day) during abstinence.	<u>Cocaine</u> : incubation of cued or cocaine-primed craving (assessed using a within-session extinction/reinstatement procedure after extended access SA and 6 weeks of abstinence).	-Low and high running similarly decreased cue-induced craving. -High running increased cocaine-primed craving.
Sanchez(50)	Adolescent male rats	Voluntary wheel running (2-hr/day) or locked-wheel access during abstinence.	<u>Nicotine</u> : incubation of cue-induced craving (assessed using a within-session extinction/reinstatement procedure after extended access SA and 10 days of abstinence).	-Decreased nicotine-craving during extinction. -Did not affect the low levels of cue-induced craving.

Withdrawal Severity/Craving				
1 st author (ref)	Subjects	Exercise Schedule	Drug and Study Design	Effect of exercise Sex differences/sex-specific effects
Sanchez(51)	Adolescent male and female rats	Voluntary wheel running (2-hr/day) or locked/no-wheel access during abstinence.	<u>Nicotine</u> : incubation of cue-induced craving (assessed using a within-session extinction/reinstatement procedure after extended access SA and 10 days of abstinence).	-Did not affect the low levels of cue-induced craving. -Decreased craving during extinction in both sexes. -Locked wheel also decreased craving in females. -Females ran more than males.
Sobieraj (52)	Male rats	Unlimited voluntary wheel running or no-wheel access during abstinence.	<u>METH</u> : incubation of context versus cue-induced craving (assessed using a between-session extinction/reinstatement procedure after extended access SA and 30 days of abstinence).	-Decreased craving during extinction and blocked context- and cue-induced increases in craving.