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Exercise as a Prevention for Substance Use Disorder: A Review of Sex Differences and Neurobiological Mechanisms

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Abstract

Purpose of Review—This report provides an update on clinical and preclinical findings for the efficacy of exercise to prevent substance use disorder with a focus on recent evidence for sex differences and neurobiological mechanisms.

Recent Findings—Exercise/physical activity is associated with decreased drug use in humans. Preclinical results further indicate that exercise decreases vulnerability to drug use and the development of features of substance use disorder, and suggest that females have an enhanced sensitivity to its reward-substitution effects. However, certain exercise conditions may sensitize the reward pathway and enhance vulnerability suggesting that parallel observations in humans (e.g., increased prescription opioid misuse and heroin use in high-school athletes) may be biologically-based.

Summary—Exercise is a promising prevention strategy for substance use disorder. Further work is needed to establish its efficacy as a sex-specific strategy using larger samples, and to understand the exercise conditions that induce beneficial versus risk-enhancing effects.

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Compliance with Ethics Guidelines

Conflict of Interest

Wendy J. Lynch, Andrea M. Robinson, Jean Abel, 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.

Keywords

acquisition; addiction; animal models; biological mechanisms; clinical; drug use initiation; drug use escalation; exercise; gender differences; gonadal hormones; intervention; physical activity; preclinical; prevention; sex differences; sex-specific; substance use disorder

Introduction

Exercise has been suggested as a prevention for substance use disorder that also has secondary health benefits (e.g., prevention of obesity; 1). It is also viewed as an attractive alternative to pharmacotherapy that can be safely used in both adult and adolescent populations (2). Exercise may be a particularly attractive option for adolescent females and women given that weight gain, which can be offset by exercise, is a significant contributor for both initiation and maintenance of drug use, particularly for stimulant drug use, in these populations (3).

Evidence supporting exercise as a prevention for substance use disorder is indicated by epidemiological data demonstrating a negative association between levels of exercise/physical activity and risk of smoking and illicit drug use in adolescent and young adult males and females (4–7). Results from studies in male and female animals corroborate these findings, and demonstrate that exercise, such as wheel and treadmill running, decrease the acquisition of drug self-administration and levels of drug use (e.g., 8). Results from preclinical studies have also shown that exercise can prevent the development of addiction-like behaviors, such escalation, or the progressive increase in drug use over time (9), indicating that exercise may not only prevent drug use initiation, but may also prevent the development of features of substance use disorder. Exercise has also been suggested as a sex-specific treatment for substance use disorder, and evidence for these effects was reviewed in Part II (10; also see 11).

Despite these promising results, recent data from both humans and animals suggest that certain exercise conditions may enhance risk of drug use (e.g., 9,12). For example, involvement in certain sports is associated with higher levels of drug and alcohol use, with findings that vary between males and females and between different sports (12–13). While such findings are likely attributable, at least in part, to socio-cultural factors (14–16), findings in animals have also revealed that certain exercise conditions enhance vulnerability to drug use and the development of features of addiction (9) suggesting that biological factors also contribute. The occurrence of protective versus risk-enhancing effects is likely determined by the underlying neurobiology (17), which can depend on a number of factors including the exercise type and schedule of availability, substance used/self-administered, phase of substance use disorder, and sex.

The objective of this report is to summarize recent findings (2012–2017) on the efficacy of exercise as a prevention for substance use disorder with the goal being to provide a better understanding of the conditions that lead to beneficial versus risk-enhancing effects. Findings from both human and animal studies are included in order to examine the biological basis for the efficacy of exercise. This review also highlights recent evidence for

sex-specific differences in the efficacy and neurobiological basis of exercise as a prevention for substance use disorder. We conclude with suggestions for future studies to help guide the development of exercise as a sex-specific prevention strategy.

Overview of recent findings in human males and females

Epidemiological studies have long reported negative associations between levels of exercise/physical activity and substance use among adolescents and young adults (for review see 17), populations known to be vulnerable to the initiation of substance use (18–19). Similar associations are also revealed in recent cross-sectional and longitudinal studies, but with effects that differ between males and females and populations/cultures (4,6–7; Table 1). For example, in Polish high-school students, regular physical activity was negatively associated with cigarette and marijuana use in males, but not females (7); whereas, in Slovak and Czech high-school students, physical activity was negatively associated with cigarette and marijuana use in females, but not males (4,6). While socio-cultural factors likely contribute these differential effects (20), levels of exercise/physical activity also differ between males and females and populations (4,6–7); thus, exercise may interact with socio-cultural factors to differentially influence the use of drugs in males versus females within different populations.

Associations between exercise/physical activity and drug use can also vary between studies based on how exercise/physical activity is defined (4–7). For example, while physical activity specifically related to exercise/sports was negatively associated with cigarette and marijuana use, overall levels of physical activity, which includes exercise/sports as well as everyday physical activities during work and leisure time, was not associated with cigarette or marijuana use, and actually predicted at-risk alcohol use (5). Furthermore, physical activity not related to exercise/sports (i.e., occupational activity) predicted an increased risk of cigarette and cannabis use (5). Sports participation is also often used as a measure of exercise, yet levels of exercise/physical activity vary widely between different sports (21), and can be well-below recommended guidelines (60 min/day of moderate to vigorous physical activity; 22) and similar to those observed in individuals not participating in sports (21).

Socio-cultural factors may also interact with exercise/physical activity to influence vulnerability to drug and alcohol use (14–16). For example, while exercise is negatively associated with alcohol, cigarette, and marijuana and other illicit drug use (16), sports participation is positively associated with smokeless tobacco and alcohol use (16,23–24; for review see 25). Associations between team sports participation and drug and alcohol use also differs between males and females and type of sport (e.g., 12–13). Perhaps most alarming are results showing that middle- and high-school athletes participating in sports associated with a high risk of injury (e.g., football and wrestling) have an increased risk of prescription opioid misuse (12;26). Higher risk of heroin use have also been reported in high-school athletes participating in these types of high-risk of injury sports (ice hockey, wrestling, weightlifting; 12). Participation in sports during high-school, even if non-contact, also predicts increased binge alcohol use during adulthood, and participation in contact-sports (e.g., football, wrestling, ice hockey) during high-school predicts not only increased

binge drinking, but also, increased marijuana use, and prescription opioid misuse during adulthood (27–28). Although these findings have been observed in samples that include both males and females, the enhanced opioid use/misuse reported is likely associated with male athletes given that the sports identified are expected to be comprised predominantly of males (also see 13). While these findings suggest that socio-cultural factors associated with team sport participation can offset the protective effects of exercise, it is also possible that biological factors induced by exercise contribute to the enhanced vulnerability.

It should be noted, however, that the majority of athletes do not participate in high-contact sports and are not at a higher risk of opioid use or misuse (29). In fact, adolescent males and females who participate in sports/exercise have lower lifetime risk of prescription opioid misuse and heroin use as compared to adolescent males and females who do not participate in sports/exercise (29). Similarly, levels of substance use among elite male and female athletes, who train for multiple hours each day, are low for not only cigarettes and illicit drugs, but also for alcohol and smokeless tobacco (30). These findings are also consistent with results showing that when physical activity was part of an intervention to increase healthy behaviors (i.e., increase physical activity and fruit and vegetable consumption; limit television watching), it decreased smoking and alcohol use initiation in both males and females and was more successful in doing so than a substance use intervention (31; but see 32).

Together, these studies suggest that exercise decreases vulnerability to drug use, particularly cigarette and illicit drug use. Instances of enhanced sensitivity have been reported in males and females involved in certain sports, and while socio-cultural factors likely contribute, it is also possible that the enhanced sensitivity is, at least in part, biologically-based.

Evidence for sex differences in humans

Although clinical and epidemiological studies typically include both males and females, small sample sizes prevent most studies from being able to determine sex differences in the association/effect of exercise/physical activity on vulnerability to drug use (27,30–32). The few recent studies that have examined sex differences have focused on middle- and high-school students, with conflicting results that vary between populations (4,6–7). Recent findings also suggest that risk of drug use from participating in certain sports differs between males and females, with evidence for reduced risk in females (13). It is possible that exercise protects against alcohol and drug use in both males and females, but that sociocultural factors associated with sports team participation interact with exercise to modify vulnerability. Thus, in females, either exercise provides greater protection against alcohol and drug use or sociocultural factors induce less risk. Further studies are needed to determine sex differences in these interactive effects using larger samples. Randomized controlled trials of exercise as a prevention for drug and alcohol use are also needed in order to establish causal effects.

Overview of recent findings in male and female animals

Animal models of exercise and drug use have allowed for an examination of the biological effects of exercise separate from potential social factors (17). Results from studies in male and female animals suggest that exercise may not only prevent drug use initiation (8), but also the development of features of addiction such as drug use escalation (9). Drug use initiation has been modeled in animals using acquisition procedures that measure how quickly animals acquire drug self-administration, and by measuring maintenance levels of intake, after acquisition has been established. Drug use escalation, or a progressive increase in drug intake over time, is believed to mimic excessive/uncontrolled drug use typical of human substance use disorder (33) and can be captured in animals by extending the access to the drug (6 hr/day). While most of this work has focused on aerobic exercise via voluntary wheel running or forced treadmill running (e.g., 34–35), recent work has examined effects of resistance exercise using a weighted ladder-climbing procedure (36).

Recent studies show that exercise decreases rates of acquisition of drug self-administration and maintenance levels of intake (8–9,34–43; Table 2). For example, concurrent unlimited access to a running wheel decreases acquisition and maintenance of alcohol consumption under 24-hr free choice conditions in both males and females, and in both rats and mice (37–39). Similarly, continuous access to a running wheel prior to and following each self-administration session decreases the acquisition and maintenance self-administration of numerous substances including methamphetamine, cocaine, heroin, and speedball (i.e., combination of heroin and cocaine); these effects have been observed in both males and females and adolescents and adults (9, 40–42). Modest exercise conditions also promote decreased acquisition and maintenance intake as demonstrated by recent findings showing that voluntary wheel running (2-hr/day) prior to each self-administration session robustly attenuates acquisition of nicotine self-administration and its reinforcing effects in male rats (8). Concurrent access to a wheel (1-hr/day) during methamphetamine self-administration sessions also decreased acquisition and maintenance intake (28), and weighted ladder-climbing (~2-hr sessions) reduced cocaine self-administration in female rats (34). While greater efficacy is observed with longer exercise access (35), individual differences within a particular condition generally do not predict the efficacy of exercise with results demonstrating beneficial effects even in animals with low exercise output (e.g., in aging hamsters, males versus females, Sprague Dawley versus Wistar rats; 34,37,43). Together, these results indicate that even a modest amount of exercise (aerobic or resistance) can reduce drug use initiation.

Recent studies also show that exercise can block drug use escalation (9,38–39,44). For example, continuous access to a wheel prior to and following each self-administration session prevents escalation of methamphetamine intake and decreases its reinforcing effects in male rats (9). Similar results have been obtained for the effects of concurrent wheel access on escalation of cocaine self-administration in adolescent female rats (44), and free-access alcohol consumption in female mice (38–39), indicating that exercise attenuates/blocks the development of features of substance use disorder. As in humans, however, effects on alcohol consumption in males are variable with results from one study showing decreased consumption (37), and another, showing no effect (39). These findings are in contrast to

those observed during acquisition, where exercise decreased alcohol consumption in both males and females (39), and suggest that its effects on alcohol differ by sex and between different phases of substance use disorder.

The efficacy of exercise at reducing drug use appears to be fairly transient (8–9,34–35,42,44). For example, while wheel running markedly suppressed responding for nicotine in males, once wheel access was removed, responding increased to no-wheel control levels within 48 hours (8). Similar results have been observed in males and females, and for both cocaine and methamphetamine self-administration (9,34–35,42,44), indicating that continuous exercise is necessary to maintain decreased drug intake. The time-line for the persistency of effects, however, may differ between substances given results showing that alcohol consumption remains decreased for up to 10-days after removal of wheel access (37). It is also possible that other factors, such as age of the population studied, underlies the persistent decrease in alcohol consumption. Further research is needed to address this possibility.

Interestingly, a long history of exercise is not necessary to reduce drug intake (42–43). For example, a single wheel running session immediately prior to drug self-administration reduced methamphetamine, methylone, and MDMA self-administration in males and females (43). However, Engleman et al. (9) found that terminating wheel running sessions prior to methamphetamine self-administration training, enhanced rates of acquisition in male rats that had a history of unlimited voluntary wheel running. Previous studies have reported similar reward-enhancing effects of exercise for cocaine in females and for morphine in males (45–46) indicating that certain exercise conditions enhance vulnerability to drugs of abuse. These findings may also explain recent observations of increased prescription opioid misuse and heroin use in certain high-school athletes (12) given that like the situation described above with rats, in human athletes, an injury would be expected to cause a break in the pattern of regular high-intensity exercise, which could then increase vulnerability to drug use. Other breaks in regular high-intensity exercise would also be expected to occur in high-school athletes, but injury may be a special case in that the likelihood of access to opioids would also be increased (13).

Together, these studies show that exercise reduces drug intake across multiple phases of substance use disorder including acquisition, maintenance, and escalation in both males and females. The protective effects of exercise are available after a single bout of exercise, and have been observed for multiple classes of drugs. Beneficial effects have also been observed following both forced and voluntary exercise indicating that exercise may not have to be rewarding to be effective. However, exercise may need to be maintained to provide protection, and its effects on alcohol are variable. Certain exercise conditions may also enhance vulnerability indicating that parallel findings in humans may be biologically-based.

Evidence for sex differences in laboratory animals

Results from the few recent studies that have compared the effects of exercise on acquisition and maintenance drug intake between males and females have reported sex differences, with exercise benefiting females more than males (39,43). Although previous results have been more variable (for review see 11), a comparison of all available studies indicates that the

occurrence of sex differences may depend on exercise access conditions. Specifically, studies investigating effects of contemporaneous, but non-concurrent exercise, generally report equal efficacy of exercise at reducing drug intake in males versus females (43,47); whereas, studies using concurrent access conditions generally report greater efficacy in females versus males (39,48). These results suggest that while males and females equally benefit from the physiological effects that occur following exercise (and that persist during daily sessions), females have an enhanced sensitivity to the reward substitution effects of exercise. This interpretation is consistent with previous work showing that concurrent access to non-drug rewards, such as palatable sweet solutions, produce greater decreases in drug intake in females as compared to males (for review see 49). Females also run at higher levels than males (e.g., 48), which both supports this idea since it demonstrates that females allocate greater time/energy to exercise as a non-drug alternative, and confounds the results since the “dose” of exercise is higher in females than males. Further work should control for sex differences in levels of exercise and include a large enough sample to ensure adequate power for the detection of sex differences. Moreover, given that ovarian hormones can influence both wheel running (50) and drug self-administration (51), additional studies are needed to determine their role in mediating the efficacy of exercise to prevent drug use.

Overview of recent findings for the neurobiological effects of exercise in males and females

The efficacy of exercise as a prevention for substance use disorder is likely mediated via interactions with mesolimbic dopamine given the critical role this pathway plays in drug use initiation and substance use disorder (52). The reinforcing effects of both drugs of abuse and exercise are dependent on activation of the mesolimbic dopamine system consisting of dopaminergic projections from the ventral tegmental area to the nucleus accumbens (NAc) and prefrontal cortex (52–54). Inactivation of this pathway decreases drug self-administration (e.g., 55), with recent findings demonstrating that such manipulations similarly disrupt wheel running in males and females (56). Several markers of mesolimbic dopaminergic signaling predict sensitivity to drug reinforcement (enhanced D1/reduced D2 signaling in NAc; 57), and recent findings indicate that such markers are also predictive of wheel running activity in males and females (excitatory/inhibitory dopamine mRNA expression in the NAc; 58). Dopamine signaling in the NAc, in particular, is critical for mediating the reinforcing effects of drugs of abuse and exercise (52–53). Thus, exercise may function as an alternative reward that competes with the drug to decrease the probability of its use.

Exercise also activates similar signaling pathways as drugs of abuse (59), and induces long-term changes in plasticity that may protect against initial vulnerability (downregulation/upregulation of D1/D2 receptors; prevent/reverse dendritic spine loss in D2-containing medium spiny neurons; 60–62). For example, chronic forced running prior to testing blocks the reinforcing effects of MDMA and MDMA-induced NAc dopamine release (63), indicating that exercise-induced adaptations may blunt the dopaminergic response to drugs of abuse. Exercise can also normalize glutamatergic signaling (64), and these effects may protect against drug use escalation and the development of substance use disorder (for review see 65). For example, chronic treadmill running reduced markers of hyper-

excitability (e.g., upregulation of GluA2/3, and downregulation of GluA1 receptors) in a Parkinson's Disease model, which is also characterized by depletion of dopamine and hyper-excitability/abnormal glutamatergic transmission (64). Exercise can also produce modifications at the level of chromatin, which induce long-term changes in gene expression (66). Effects on chromatin containing the Bdnf gene in particular has been implicated in mediating persistent protection against drug use, particularly in males (67). Both drugs of abuse and exercise modulate Bdnf (68–69), and recent evidence show that resistance exercise affects drug-induced changes in Bdnf expression in female rats (36).

Preclinical evidence also indicates that certain exercise conditions can mimic the effects of chronic drug exposure (downregulating D2 receptors in NAc; 53), and sensitize the reward pathway to later drug use. Similar effects may underlie vulnerability reported in rats with a history of high access/intense exercise (9). These findings suggest that cessation of regular exercise at a high level, which can also occur in human athletes following injury, may increase subsequent vulnerability to drugs by sensitizing the reward pathway.

Evidence for sex differences in the neurobiological effects of exercise

There are likely sex differences in the neurobiological effects of exercise given behavioral evidence suggesting enhanced efficacy in females versus males, particularly under concurrent access conditions (39,48). This effect is likely reflective of a general increase in sensitivity to rewarding stimuli in females (49). Given work demonstrating sex differences in the effects of drugs of abuse and natural rewards on mesolimbic dopaminergic signaling (70), it is possible that exercise may also induce a greater dopaminergic response in females versus males. It is also possible that, by running at higher levels, females induce/maintain greater activation of mesolimbic dopamine. Future research is needed to address these possibilities.

Most studies examining the neurobiological basis for the efficacy of exercise have focused on males or females and on dopaminergic signaling following stimulant use/exposure (53). Future research is needed to address sex differences and the role of other signaling pathways, such as opioid, endocannabinoid, and Bdnf, given that each pathway contributes to the reinforcing effects of exercise and drugs of abuse (71–72).

Conclusions and Future Directions

Epidemiological data demonstrate that engagement in exercise-related activities is associated with a lower risk of drug use, particularly cigarette and illicit drug use (4–7,16,30). Animal studies have consistently shown that exercise decreases drug use during multiple phases including acquisition, maintenance, and escalation (34–44) indicating its potential as a prevention for substance use disorder. Beneficial effects have been reported for both males and females (39,43,47–48), with evidence suggesting that females have an enhanced sensitivity to the reward-substitution effects of exercise as compared to males (39,48). However, future studies that include larger samples and that control for levels of exercise are needed to confirm this possibility. Concomitant with these studies, investigators should examine interventions that increase adherence to exercise, given that girls are less physically active than boys (73), and given that physical activity decreases throughout adolescence in

both girls and boys (74). Such efforts may be critical considering the preclinical results showing that continuous exercise is necessary to maintain beneficial effects (8–9).

While effects on alcohol are also promising, they are variable (37–39). However, it is important to note that the recent preclinical results show that exercise either decreases or does not affect alcohol consumption (37–39). This is important because it suggests that the increased alcohol use reported in boys and girls participating in certain sports is driven by sociocultural factors rather than biological factors. Future research is needed to determine the exercise conditions that consistently and robustly decrease vulnerability to alcohol and other drug use in males and females. A better understanding of the neurobiological mechanisms that mediate the efficacy of exercise to decrease vulnerability to drug use is also needed in order to determine how to maximize its beneficial effects (e.g., in combination with pharmacological interventions).

Despite these promising results, both clinical and preclinical results suggest that certain exercise conditions may enhance vulnerability to drug use (9). Future research is needed to understand the underlying mechanisms for these effects so that interventions can be developed to prevent the enhanced vulnerability. For example, if cessation of regular high-intensity exercise sensitizes the reward pathway, then potential solutions to prevent the increase in vulnerability to drug use (9,12) may include modified-exercise interventions, environmental enrichment, or brief educational interventions (75–77).

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References

1. Greer TL, Ring KM, Warden D, Grannemann BD, Church TS, Somoza E, Blair SN, Szapocznik J, Stoutenberg M, Rethorst C, Walker R, Morris DW, Kosinski AS, Kyle T, Marcus B, Crowell B, Oden N, Nunes E, Trivedi MH. Rationale for using exercise in the treatment of stimulant use disorders. *J Glob Drug Policy Pract.* 2012; 6(1)
2. Linke SE, Ussher M. Exercise-based treatments for substance use disorders: evidence, theory, and practicality. *Am J Drug Alcohol Abuse.* 2015; 41(1):7–15. [PubMed: 25397661]
3. Tuchman E. Women and Addiction: The importance of gender issues in substance abuse research. *J Addict Dis.* 2010; (2):127–138. [PubMed: 20407972]
4. Ham ík Z, Bobáková D, Kalman M, Veselská ZD, Klein D, Gecková AM. Physical activity and screen-based activity in healthy development of school-aged children. *Cent Eur J Public Health.* 2015; 23(Suppl):S50–6. [PubMed: 26849544]
5. Henchoz Y, Dupuis M, Deline S, Studer J, Baggio S, N'Goran AA, Daeppen JB, Gmel G. Associations of physical activity and sport and exercise with at-risk substance use in young men: a longitudinal study. *Prev Med.* 2014; 64:27–31. [PubMed: 24704130]
6. Lesjak V, Stanojevi -Jerkovi O. Physical activity, sedentary behavior and substance use among adolescents in Slovenian urban area. *Zdr Varst.* 2015; 54(3):168–74. [PubMed: 27646724]
7. Tabak I, Mazur J, Zawadzka D. Physical activity as a factor protecting teenage boys from tobacco and marijuana use. *Przegl Epidemiol.* 2015; 69(4):795–800. 919–22.
8. Sanchez V, Lycas MD, Lynch WJ, Brunzell DH. Wheel running exercise attenuates vulnerability to self-administer nicotine in rats. *Drug Alcohol Depend.* 2015; 156:193–8. [PubMed: 26433561]
9. Engelmann AJ, Aparicio MB, Kim A, Sobieraj JC, Yuan CJ, Grant Y, Mandyam CD. Chronic wheel running reduces maladaptive patterns of methamphetamine intake: regulation by

attenuation of methamphetamine-induced neuronal nitric oxide synthase. *Brain Struct Funct*. 2014; 219(2):657–72. This study showed that terminating exercise sessions prior to methamphetamine self-administration training, enhanced rates of acquisition in rats that had a history of unlimited voluntary wheel running indicating that certain exercise conditions enhance vulnerability to drugs of abuse. [PubMed: 23443965]

10. Lynch WJ, Abel J, Robinson AM, Smith MA. Part II: Exercise as a treatment for substance use disorder: a review of sex differences and neurobiological mechanisms. *Curr Addict Reports*. submitted.
11. Zhou Y, Zhao M, Zhou C, Li R. Sex differences in drug addiction and response to exercise intervention: From human to animal studies. *Front Neuroendocrinol*. 2016; 40:24–41. [PubMed: 26182835]
12. Veliz P, Boyd CJ, McCabe SE. Nonmedical use of prescription opioids and heroin use among adolescents involved in competitive sports. *J Adolesc Health*. 2017; 60(3):346–349. This study showed high-school participation in certain sports where risk of injury is high (e.g., football, ice hockey, lacrosse, and wrestling) is associated with increased *prescription opioid misuse* and heroin. [PubMed: 27914974]
13. Veliz P, Epstein-Ngo QM, Meier E, Ross-Durow PL, McCabe SE, Boyd CJ. Painfully obvious: a longitudinal examination of medical use and misuse of opioid medication among adolescent sports participants. *J Adolesc Health*. 2014; 54(3):333–40. [PubMed: 24225446]
14. Fujimoto K, Unger JB, Valente TW. A network method of measuring affiliation-based peer influence: assessing the influences of teammates' smoking on adolescent smoking. *Child Dev*. 2012; 83(2):442–51. [PubMed: 22313152]
15. Kwan M, Bobko S, Faulkner G, Donnelly P, Cairney J. Sport participation and alcohol and illicit drug use in adolescents and young adults: a systematic review of longitudinal studies. *Addict Behav*. 2014; 39(3):497–506. [PubMed: 24290876]
16. Terry-McElrath YM, O'Malley PM, Johnston LD. Exercise and substance use among American youth, 1991–2009. *Am J Prev Med*. 2011; 40(5):530–40. [PubMed: 21496752]
17. Lynch WJ, Peterson AB, Sanchez V, Abel J, Smith MA. Exercise as a novel treatment for drug addiction: a neurobiological and stage-dependent hypothesis. *Neurosci Biobehav Rev*. 2013; 37(8):1622–44. [PubMed: 23806439]
18. Gray KM, Squeglia LM. What have we learned about adolescent substance use? *J Child Psychol Psychiatry*. 2017 [Epub ahead of print].
19. Stone AL, Becker LG, Huber AM, Catalano RF. Review of risk and protective factors of substance use and problem use in emerging adulthood. *Addict Behav*. 2012; 37(7):747–75. [PubMed: 22445418]
20. Vari R, Scaccocchio B, D'Amore A, Giovannini C, Gessani S, Masella R. Gender-related differences in lifestyle may affect health status. *Ann Ist Super Sanita*. 2016; 52(2):158–66. [PubMed: 27364389]
21. Hebert JJ, Møller NC, Andersen LB, Wedderkopp N. Organized sport participation is associated with higher levels of overall health-related physical activity in children (CHAMPS Study-DK). *PLoS One*. 2015; 10(8):e0134621. [PubMed: 26262678]
22. World Health Organization. Global recommendations on physical activity for health. Vol. 2010. Geneva, Switzerland: World Health Organization; 2010. Report No.: 9789241599979
23. Lisha NE, Crano WD, Delucchi KL. Participation in team sports and alcohol and marijuana use initiation trajectories. *J Drug Issues*. 2014; 44(1):83–93. [PubMed: 26594059]
24. Mattila VM, Raisamo S, Pihlajamäki H, Mäntysaari M, Rimpelä A. Sports activity and the use of cigarettes and snus among young males in Finland in 1999–2010. *BMC Public Health*. 2012; 12:230. [PubMed: 22439614]
25. Lisha NE, Sussman S. Relationship of high school and college sports participation with alcohol, tobacco, and illicit drug use: a review. *Addict Behav*. 2010; 35(5):399–407. [PubMed: 20100638]
26. Veliz PT, Boyd C, McCabe SE. Playing through pain: sports participation and nonmedical use of opioid medications among adolescents. *Am J Public Health*. 2013; 103(5):e28–30.
27. Veliz P, Schulenberg J, Patrick M, Kloska D, McCabe SE, Zarrett N. Competitive sports participation in high school and subsequent substance use in young adulthood: Assessing

- differences based on level of contact. *Int Rev Sociol Sport*. 2017; 52(2):240–259. [PubMed: 28344426]
28. Veliz P, McCabe SE. Examining potential substance use disorders among former interscholastic athletes. *Subst Abus*. 2015; 36(4):400–6. [PubMed: 25551424]
 29. Veliz P, Boyd CJ, McCabe SE. Nonmedical prescription opioid and heroin use among adolescents who engage in sports and exercise. *Pediatrics*. 2016 Aug.138(2) pii: e20160677. doi: 10.1542/peds.2016-0677
 30. Martinsen M, Sundgot-Borgen J. Adolescent elite athletes' cigarette smoking, use of snus, and alcohol. *Scand J Med Sci Sports*. 2014; 24(2):439–46. [PubMed: 22830488]
 31. Velicer WF, Redding CA, Paiva AL, Mauriello LM, Blissmer B, Oatley K, Meier KS, Babbitt SF, McGee H, Prochaska JO, Burditt C, Fernandez AC. Multiple behavior interventions to prevent substance abuse and increase energy balance behaviors in middle school students. *Transl Behav Med*. 2013; 3(1):82–93. [PubMed: 23585821]
 32. Weinstock J, Capizzi J, Weber SM, Pescatello LS, Petry NM. Exercise as an intervention for sedentary hazardous drinking college students: A pilot study. *Ment Health Phys Act*. 2014; 7(1): 55–62. [PubMed: 24949085]
 33. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5. Arlington, VA: American Psychiatric Publishing; 2013.
 34. Miller ML, Vaillancourt BD, Wright MJ Jr, Aarde SM, Vandewater SA, Creehan KM, Taffe MA. Reciprocal inhibitory effects of intravenous d-methamphetamine self-administration and wheel activity in rats. *Drug Alcohol Depend*. 2012; 121(1–2):90–6. [PubMed: 21899959]
 35. Smith MA, Fronk GE, Zhang H, Magee CP, Robinson AM. Acute bouts of wheel running decrease cocaine self-administration: Influence of exercise output. *Pharmacol Biochem Behav*. 2016; 150–151:94–99.
 36. Strickland JC, Abel JM, Lacy RT, Beckmann JS, Witte MA, Lynch WJ, Smith MA. The effects of resistance exercise on cocaine self-administration, muscle hypertrophy, and BDNF expression in the nucleus accumbens. *Drug Alcohol Depend*. 2016; 163:186–94. [PubMed: 27137405]
 37. Brager AJ, Hammer SB. Impact of wheel running on chronic ethanol intake in aged Syrian hamsters. *Physiol Behav*. 2012; 107(3):418–23. [PubMed: 23022151]
 38. Darlington TM, McCarthy RD, Cox RJ, Miyamoto-Ditmon J, Gallego X, Ehringer MA. Voluntary wheel running reduces voluntary consumption of ethanol in mice: identification of candidate genes through striatal gene expression profiling. *Genes Brain Behav*. 2016; 15(5):474–90. [PubMed: 27063791]
 39. Gallego X, Cox RJ, Funk E, Foster RA, Ehringer MA. Voluntary exercise decreases ethanol preference and consumption in C57BL/6 adolescent mice: sex differences and hippocampal BDNF expression. *Physiol Behav*. 2015; 138:28–36. [PubMed: 25447477]
 40. Lacy RT, Strickland JC, Brophy MK, Witte MA, Smith MA. Exercise decreases speedball self-administration. *Life Sci*. 2014; 114(2):86–92. [PubMed: 25132360]
 41. Smith MA, Pitts EG. Wheel running decreases the positive reinforcing effects of heroin. *Pharmacol Rep*. 2012; 64(4):960–4. [PubMed: 23087148]
 42. Smith MA, Witte MA. The effects of exercise on cocaine self-administration, food-maintained responding, and locomotor activity in female rats: importance of the temporal relationship between physical activity and initial drug exposure. *Exp Clin Psychopharmacol*. 2012; 20(6):437–46. [PubMed: 22924703]
 43. Aarde SM, Miller ML, Creehan KM, Vandewater SA, Taffe MA. One day access to a running wheel reduces self-administration of D-methamphetamine, MDMA and methylone. *Drug Alcohol Depend*. 2015; 151:151–8. [PubMed: 25863714]
 44. Zlebnik NE, Anker JJ, Carroll ME. Exercise to reduce the escalation of cocaine self-administration in adolescent and adult rats. *Psychopharmacology*. 2012; 224(3):387–400. [PubMed: 22752381]
 45. Eisenstein SA, Holmes PV. Chronic and voluntary exercise enhances learning of conditioned place preference to morphine in rats. *Pharmacol Biochem Behav*. 2007; 86(4):607–15. [PubMed: 17368736]

46. Smith MA, Gergans SR, Iordanou JC, Lyle MA. Chronic exercise increases sensitivity to the conditioned rewarding effects of cocaine. *Pharmacol Rep.* 2008; 60(4):561–5. [PubMed: 18799826]
47. Smith MA, Walker KL, Cole KT, Lang KC. The effects of aerobic exercise on cocaine self-administration in male and female rats. *Psychopharmacology.* 2011; 218(2):357–69. [PubMed: 21567123]
48. Cosgrove KP, Hunter RG, Carroll ME. Wheel-running attenuates intravenous cocaine self-administration in rats: sex differences. *Pharmacol Biochem Behav.* 2002; 73(3):663–71. [PubMed: 12151042]
49. Carroll ME, Smethells JR. Sex differences in behavioral dyscontrol: role in drug addiction and novel treatments. *Front Psychiatry.* 2016; 6:175. [PubMed: 26903885]
50. Anantharaman-Barr HG, Decombaz J. The effect of wheel running and the estrous cycle on energy expenditure in female rats. *Physiol Behav.* 1989; 46(2):259–63. [PubMed: 2602468]
51. Carroll ME, Lynch WJ. How to study sex differences in addiction using animal models. *Addict Biol.* 2016; 21(5):1007–29. [PubMed: 27345022]
52. Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci.* 1988; 85(14):5274–8. [PubMed: 2899326]
53. Greenwood BN, Foley TE, Le TV, Strong PV, Loughridge AB, Day HE, Fleshner M. Long-term voluntary wheel running is rewarding and produces plasticity in the mesolimbic reward pathway. *Behav Brain Res.* 2011; 217(2):354–62. [PubMed: 21070820]
54. Herrera JJ, Fedynska S, Ghasem PR, Wieman T, Clark PJ, Gray N, Loetz E, Campeau S, Fleshner M, Greenwood BN. Neurochemical and behavioural indices of exercise reward are independent of exercise controllability. *Eur J Neurosci.* 2016; 43(9):1190–202. [PubMed: 26833814]
55. Singer G, Wallace M. Effects of 6-OHDA lesions in the nucleus accumbens on the acquisition of self injection of heroin under schedule and non schedule conditions in rats. *Pharmacol Biochem Behav.* 1984; 20(5):807–9. [PubMed: 6429675]
56. Basso JC, Morrell JJ. The medial prefrontal cortex and nucleus accumbens mediate the motivation for voluntary wheel running in the rat. *Behav Neurosci.* 2015; 129(4):457–72. [PubMed: 26052795]
57. Ashok AH, Mizuno Y, Volkow ND, Howes OD. Association of stimulant use with dopaminergic alterations in users of cocaine, amphetamine, or methamphetamine: a systematic review and meta-analysis. *JAMA Psychiatry.* 2017; 74(5):511–519. [PubMed: 28297025]
58. Park YM, Kanaley JA, Padilla J, Zidon T, Welly RJ, Will MJ, Britton SL, Koch LG, Rueggsegger GN, Booth FW, Thyfault JP, Vieira-Potter VJ. Effects of intrinsic aerobic capacity and ovariectomy on voluntary wheel running and nucleus accumbens dopamine receptor gene expression. *Physiol Behav.* 2016; 164(Pt A):383–9. [PubMed: 27297873]
59. Zlebnik NE, Hedges VL, Carroll ME, Meisel RL. Chronic wheel running affects cocaine-induced c-Fos expression in brain reward areas in rats. *Behav Brain Res.* 2014; 261:71–8. [PubMed: 24342748]
60. Chen W, Wang HJ, Shang NN, Liu J, Li J, Tang DH, Li Q. Moderate intensity treadmill exercise alters food preference via dopaminergic plasticity of ventral tegmental area-nucleus accumbens in obese mice. *Neurosci Lett.* 2017; 641:56–61. [PubMed: 28130186]
61. Obici S, Magrisso IJ, Ghazarian AS, Shirazian A, Miller JR, Loyd CM, Begg DP, Krawczewski Carhuatanta KA, Haas MK, Davis JF, Woods SC, Sandoval DA, Seeley RJ, Goodyear LJ, Pothos EN, Mul JD. Moderate voluntary exercise attenuates the metabolic syndrome in melanocortin-4 receptor-deficient rats showing central dopaminergic dysregulation. *Mol Metab.* 2015; 4(10):692–705. [PubMed: 26500841]
62. Toy WA, Petzinger GM, Leyshon BJ, Akopian GK, Walsh JP, Hoffman MV, Vu kovi MG, Jakowec MW. Treadmill exercise reverses dendritic spine loss in direct and indirect striatal medium spiny neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. *Neurobiol Dis.* 2014; 63:201–9. [PubMed: 24316165]

63. Chen HI, Kuo YM, Liao CH, Jen CJ, Huang AM, Cherng CG, Su SW, Yu L. Long-term compulsive exercise reduces the rewarding efficacy of 3,4-methylenedioxymethamphetamine. *Behav Brain Res.* 2008; 187(1):185–9. [PubMed: 17949827]
64. Garcia PC, Real CC, Britto LR. The impact of short and long-term exercise on the expression of Arc and AMPARs during evolution of the 6-hydroxy-dopamine animal model of Parkinson's Disease. *J Mol Neurosci.* 2017; 61(4):542–552. [PubMed: 28243821]
65. Edwards S, Koob GF. Escalation of drug self-administration as a hallmark of persistent addiction liability. *Behav Pharmacol.* 2013; 24(5–6):356–62. [PubMed: 23839030]
66. Abel JL, Rissman EF. Running-induced epigenetic and gene expression changes in the adolescent brain. *Int J Dev Neurosci.* 2013; 31(6):382–90. [PubMed: 23178748]
67. Pierce RC, Vassoler FM. Reduced cocaine reinforcement in the male offspring of cocaine-experienced sires. *Neuropsychopharmacology.* 2014; 39(1):238.
68. Zoladz JA, Pilc A. The effect of physical activity on the brain derived neurotrophic factor: from animal to human studies. *J Physiol Pharmacol.* 2010; 61(5):533–41. [PubMed: 21081796]
69. Xu X, Ji H, Liu G, Wang Q, Liu H, Shen W, Li L, Xie X, Zhou W, Duan S. A significant association between BDNF promoter methylation and the risk of drug addiction. *Gene.* 2016; 584(1):54–9. [PubMed: 26976342]
70. Yoest KE, Cummings JA, Becker JB. Estradiol, dopamine and motivation. *Cent Nerv Syst Agents Med Chem.* 2014; 14(2):83–9. [PubMed: 25540977]
71. Befort K. Interactions of the opioid and cannabinoid systems in reward: Insights from knockout studies. *Front Pharmacol.* 2015; 6:6. [PubMed: 25698968]
72. Roberts MD, Ruegsegger GN, Brown JD, Booth FW. Mechanisms associated with physical activity behavior: insights from rodent experiments. *Exerc Sport Sci Rev.* 2017 [Epub ahead of print].
73. Telford RM, Telford RD, Olive LS, Cochrane T, Davey R. Why are girls less physically active than boys? Findings from the LOOK Longitudinal Study. *PLoS One.* 2016; 11(3):e0150041. [PubMed: 26960199]
74. Dumith SC, Gigante DP, Domingues MR, Kohl HW 3rd. Physical activity change during adolescence: a systematic review and a pooled analysis. *Int J Epidemiol.* 2011; 40(3):685–98. [PubMed: 21245072]
75. Horn K, Dino G, Branstetter SA, Zhang J, Noerachmanto N, Jarrett T, Taylor M. Effects of physical activity on teen smoking cessation. *Pediatrics.* 2011; 128(4):e801–11. [PubMed: 21930544]
76. Paukste E, Harris N. Using rap music to promote adolescent health: pilot study of VoxBox. *Health Promot J Austr.* 2015; 26(1):24–6. 28–9. [PubMed: 25832899]
77. Schaus JF, Sole ML, McCoy TP, Mullett N, O'Brien MC. Alcohol screening and brief intervention in a college student health center: a randomized controlled trial. *J Stud Alcohol Drugs Suppl.* 2009 Jul.(16):131–41. [PubMed: 19538921]

Evidence for Exercise as a Prevention for Substance Use Disorder: Human Studies

Table 1

1 st author (ref)	Subjects	Exercise Schedule	Study Design	Effect of exercise Sex differences/sex-specific effects
Tabak (7)	High school students between 14.6 and 16.5 years old (N=1,484; 52.8% female; Poland).	Self-reported frequency (days/week) of moderate-to-vigorous physical activity (increased heart rate and loss of breath).	Cross-sectional survey (<i>Health Behaviour in School-aged Children</i>): Association of moderate/intense physical activity and current use of tobacco, alcohol, marijuana (past 30-days).	In females: -Lower levels of physical activity than males. -No association between physical activity and tobacco, alcohol, or marijuana use. In males: -Negative association of physical activity and tobacco and marijuana use, but not alcohol use. -Decreased cigarette and marijuana use in individuals reporting 4 days/week of moderate physical activity.
Hamík (4)	Middle and high school Slovak (n=4,610; 52% female) and Czech (n=4,404; 51% female) 11, 13, and 15 year old students.	Self-reported vigorous physical activity (out of breath/sweat; 2–3 times a week).	Cross-sectional survey (<i>Health Behaviour in School-aged Children</i>): Association of vigorous physical activity and risky substance use (weekly cigarette use and lifetime drunkenness).	- Higher prevalence of vigorous physical activity, weekly smoking, and lifetime drunkenness in Czech versus Slovak adolescents. -No association of vigorous physical activity and lifetime drunkenness. -Negative association between vigorous physical activity and smoking in females, but not males.
Lesjak (6)	High school students between 14 and 16 years old (N=822; 57.7% female; Slovenia).	Self-reported physical activity (number of days/week physically active, 1-hr of physical activity/day), and vigorous physical activity (2-hr/week).	Cross-sectional survey (<i>European Urban Health Indicators System Part 2</i>): Associations between physical activity and daily cigarette use, lifetime intoxication, and lifetime cannabis use.	-Overall, reduced risk of smoking with daily or vigorous activity. In females: -Reduced risk of smoking, cannabis use and intoxication with vigorous and/or daily activity. In males: -No association between physical activity and alcohol, cigarette, or cannabis use.
Henchoz (5)	Young men (~20 years old) entering military service (N=4,748; Switzerland).	Self-reported sports/exercise participation and levels of physical activity (occupational and leisure time).	Cross-sectional and prospective survey (<i>Cohort Study on Substance Use Risk Factors</i>): Association of sports/exercise/physical activity and at-risk cigarette, cannabis, and alcohol use at baseline and 15 months later.	-Negative association between sports/exercise and at-risk cigarette and cannabis use at both time-points. -No association of sports/exercise and alcohol use. -Positive association between at-risk alcohol and levels of physical activity (including sports and exercise). -Positive association of at-risk cigarette and cannabis use with physical activity adjusted for sports/exercise.
Lisha (23)	National sample of children and adolescents (9–18 years old) (N= 8,179; 48.7% female; USA).	Self-reported sports participation in the past 12-months.	Cross-sectional and prospective survey (<i>National Survey of Parents and Youth</i>): Association between sports participation and marijuana and alcohol use trajectories over a 4-year period.	Sports participation: -Reduced risk of initial marijuana use in both males and females. -Was not related to initial alcohol use, but increased risk of alcohol use over time in both males and females.
Mattila (24)	Young men (~19 years old) entering military service (N=4,748; Finland).	Self-reported sports participation (1/week) and sport type in the past 6 months.	Health survey on the first day of military duty: Association between sports activity/type of sport and cigarette and snus use.	-Sports participation was positively associated with snus use, but negatively associated with smoking. -Sports participation, particularly ice hockey, was associated with snus and dual snus/cigarette use, but not cigarette use alone.

1 st author (ref)	Subjects	Exercise Schedule	Study Design	Effect of exercise Sex differences/sex-specific effects
Veliz (12)	National sample of 12 th grade students (18 cohorts; N=21,557; 50.6% female; USA).	Self-reported sports participation and type of sport in the past 12-months.	Cross-sectional survey (<i>Monitoring the Future</i>): Association between sports participation and past-year heroin or prescription opioid use.	-Overall, sports participation was not associated with past-year prescription opioid or heroin use. -Ice hockey participation was associated with increased risk of heroin use and concurrent prescription opioid and heroin use. -Participation in wrestling and weightlifting was associated with increased risk of heroin and prescription opioid use. -No analysis of sex difference; sports identified likely comprised predominantly of male athletes.
Veliz (26)	National sample of 8 th and 10 th grade students (2 cohorts; N=13,636; sex not specified; USA)	Self-reported sports participation and type of sport in the past 12-months.	Cross-sectional survey (<i>Monitoring the Future</i>): Association between sports participation and past-year heroin/prescription opioid misuse.	-Overall, sports participation was not associated with risk of prescription opioid misuse. -Participation in football and wrestling were associated with a 50% increase risk of prescription opioid misuse. -No analysis of sex difference; sports identified likely to include predominantly male samples.
Veliz (27)	National sample of 12 th grade students (6 cohorts; N=970; 58.6% female; USA).	Self-reported sports (1 sport) and high-contact sports participation (football, ice hockey, lacrosse, and wrestling) in the past year.	Prospective survey (<i>Monitoring the Future</i>): Association between sports participation and binge drinking, cigarette, marijuana, and illicit drug use (past 30 days) during young adulthood (1 to 4 years after the 12 th grade).	Overall sports and non-contact sports during 12 th grade: -Increased risk of binge drinking in adulthood. -Not associated with cigarette, marijuana, or illicit drug use. -High-contact sports during 12 th grade: -Increased risk of binge drinking and marijuana use in adulthood. -No sex differences, but not powered to detect interactive effects.
Veliz (28)	Sample of full-time undergraduate students (N=4,187; 57% female; USA)	Retrospective self-reported involvement in junior varsity or varsity sports during high school.	Web-based retrospective survey: Association between high school sports participation and prescription opioid use/misuse in lifetime.	-Sports participation during high school was associated with increased risk of prescription opioid use and misuse. -No sex differences.
Veliz (13)	Middle and high school students recruited from one of 5 schools during the 7 th through 10 th grade (N=4,158; 48% female; USA).	Self-reported sports participation and type of sport during this school year.	Web-based prospective survey (<i>Secondary Student Life Survey</i>): Association between sports participation and past year prescription opioid use or misuse assessed over a 3-year period.	<u>In females:</u> -No association was observed for sports participation and prescription opioid use or misuse. <u>In males:</u> -Sports participation was associated with an increased risk of prescription opioid use and misuse. -Males who participated in sports during each of the 3 years were at highest risk.
Veliz (29)	National sample of 8 th and 10 th grade students (9 cohorts; N=191,660; 51.2% female; USA).	Self-reported regular (1 day/week) or daily participation in sports, athletics, or exercise.	Cross-sectional survey (<i>Monitoring the Future</i>): Association between regular exercise/sports participation and initiation/lifetime prescription opioid misuse and heroin use.	-Higher levels of sports/exercise were associated with reduced risk of lifetime prescription opioid misuse and heroin use. -Higher levels of sports/exercise were associated with reduced risk of initiating prescription opioid misuse before heroin use. -No analysis of sex difference.
Martinsen (30)	Elite sport high school athletes (N=602) and age-matched controls (N=421; sex not specified; Norway).	Elite athletes trained ~15 hrs/week and physically active controls (54% reported 1 hour/day of moderate activity)	Questionnaire: Cigarettes, snus, alcohol, performance-enhancing illicit drug use (no, occasionally, every day) in elite athletes versus physically active controls.	-Lower cigarette, snus, alcohol, and illicit drug use in elite athletes versus controls. -Higher drinking in female versus male athletes.
Velicer (31)	Middle school students recruited from one of 20 schools during the sixth grade	Computer-delivered intervention (5, 30-min sessions over 3-years) targeting energy balance behaviors	School-based randomized trial comparing an energy balance intervention that included a physical activity component to a substance use intervention with health	Energy balance versus substance use group had: -Lower rates of smoking and alcohol use initiation at each of the follow-up assessments.

1 st author (ref)	Subjects	Exercise Schedule	Study Design	Effect of exercise Sex differences/sex-specific effects
	(N=4,158; 48% female; USA).	including physical activity (60 min., 5 days/week).	risks (cigarette and alcohol use) assessed at baseline and then at 12, 24, and 36 months.	-Higher levels of physical activity at the 24- and 36-month assessment. -No analysis of sex differences.
Weinstock (32)	Sedentary hazardous drinking young adult, college students (N=31; 65% female; 18–27 years; USA)	1, 50-min session of motivational therapy to increase exercise plus 8 weeks of contingency management to reinforce exercise.	Randomized pilot comparing the effects of motivational therapy alone or in combination with contingency management. Primary measures were exercise adherence, levels of exercise, and alcohol use.	-Well-received intervention (86.8% session attendance) -Levels of exercise were not increased by contingency management, and no effect was observed on alcohol use (drinking days, binge episodes, or drinks/week). -No analysis of sex differences.

Table 2
Evidence for Exercise as a Prevention for Substance Use Disorder: Animal Models

1 st author (ref)	Subjects	Exercise Schedule	Study Design	Effect of exercise
Miller (34)	Male rats	Voluntary wheel running (1-hr/day) as compared to unlocked or no wheel access concurrent with self-administration (SA) sessions 1–14, 8–21, or 15–21.	Acquisition and maintenance of methamphetamine SA (1-hr/day, fixed-ratio 1, FR1, 21 days) in 2 rat strains (Wistar, Sprague Dawley).	-Decreased acquisition and intake when the wheel was concurrently available. -Continued access was necessary to maintain reduced intake. -No effect on intake if introduced after acquisition. -Similar effects in both strains despite differences in running.
Smith (35)	Female rats	Forced wheel running (0, 30, 60 min) immediately or 12-hr prior to SA sessions.	Maintenance cocaine SA (2-hr/day, FR1)	-“Dose-dependently” reduced cocaine SA. -No effect when exercise occurred 12-hr prior to SA session.
Strickland (36)	Female rats	Resistance exercise (6, ~2-hr sessions/week; weighted ladder climbing; 3-set “pyramid”; 8/6/4, 70/85/100% of body weight) as compared to no exercise prior to (~14-hr) each SA session.	Maintenance cocaine SA (2-hr/day, FR1) following acquisition.	-Decreased the reinforcing effects of cocaine across a range of doses.
Brager (37)	Aging male hamsters	Concurrent unlimited voluntary wheel running (30 days) as compared to locked wheel access following acquisition of alcohol consumption.	Free-access alcohol consumption (24-hr access; 2-bottle free choice)	-Decreased free-access alcohol consumption. -Further decreased already low preference for alcohol. -Effects persisted after wheel access discontinued (10 days).
Darlington (38)	Female mice	Concurrent unlimited voluntary wheel running (16 days) as compared to no wheel access during acquisition and free-access alcohol consumption.	Acquisition and free-access consumption of alcohol (24-hr access; 2-bottle choice)	-Decreased alcohol consumption and preference throughout the 16-day consumption phase.
Gallego (39)	Adolescent male and female mice	Concurrent unlimited voluntary wheel running (21 days) as compared to no wheel access during acquisition and free-access alcohol consumption.	Acquisition and free-access consumption of alcohol (24-hr access; 2-bottle choice)	-Decreased alcohol preference, particularly in females and during acquisition. -Decreased alcohol consumption in females, but not males. -Efficacy of exercise was positively associated with distance run in females but not males.
Engelmann (9)	Male rats	Unlimited voluntary wheel running as compared to no wheel access prior to SA training (6 weeks) with or without continued wheel access prior to and following each SA session.	Acquisition, escalation (1 versus 6-hr/day; FR1), and subsequent motivation for methamphetamine (progressive-ratio, PR).	-Decreased acquisition, escalation, and motivation for methamphetamine when available prior to each session. -Markedly enhanced acquisition if discontinued prior to SA. -Continued access was necessary to prevent escalation and reduce motivation.
Lacy (40)	Female rats	Unlimited voluntary wheel running as compared to no wheel access prior to SA training (6 weeks) and prior to and following each SA session.	Maintenance cocaine, heroin, and speedball SA (PR) following acquisition.	-Decreased the reinforcing effects of cocaine, heroin, and speedball across a range of doses.
Smith (41)	Male rats	Unlimited voluntary wheel running as compared to no wheel access prior to SA training (6 weeks) and prior to and following each SA session.	Maintenance heroin SA (2-hr/day, FR1) following acquisition.	-Decreased maintenance SA.
Smith (42)	Female rats	Unlimited voluntary wheel running versus no wheel access prior to SA training (6 weeks) with or without continued exposure prior to and following each SA session.	Maintenance cocaine SA (PR) following acquisition.	-Decreased cocaine’s reinforcing effects when available before each session. -No effect if discontinued prior to SA. -No additional effect of pretraining.
Sanchez (8)	Adolescent male rats	Voluntary wheel running (2-hr/day) as compared to locked or no wheel access prior to each SA session.	Acquisition (20 infusions/session, FR1) and maintenance nicotine SA (PR).	-Prevented acquisition of nicotine SA. -Decreased nicotine’s reinforcing effects. -Effect on intake dissipated after wheel access discontinued (within 48-hr).

1 st author (ref)	Subjects	Exercise Schedule	Study Design	Effect of exercise
				-Efficacy was positively associated with level of running.
Aarde (43)	Male and female rats	Voluntary wheel running (~22 hr) as compared to no wheel access prior to SA sessions.	Maintenance methylone, methamphetamine, and MDMA SA (FR1-3, PR) following acquisition.	-Decreased methamphetamine, MDMA and methylone SA in both males and females. -Efficacy was not associated with levels of running. -Greater efficacy at reducing methylone SA in females.
Zlebnik (44)	Adolescent and adult female rats	Concurrent voluntary wheel running (16 days) as compared to locked wheel access during SA sessions with 10 additional sessions run under reversed wheel access conditions.	Escalation of cocaine SA (6-hr/dy; FR1).	-Reduced cocaine SA and escalation in adolescent rats. -Effective in adolescents even if introduced after escalation. -Concurrent access was necessary to maintain reduced intake. -Escalation did not occur in adults, and as such, no effect of exercise in adults.