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# *DRUG ADDICTION PREVENTION BY PHYSICAL EXERCISE*

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**Abstract**

This review aims to describe the current knowledge about physical exercise use on drug addiction management, principally in prevention. The following searching terms in PubMed were used: [“drug addiction” AND “physical exercise” AND “prevention”] or [“drug addiction prevention” AND “physical exercise]. Relevant references from key publications and gray literature were also reviewed to identify additional citations for inclusion. Also the references of articles were also reviewed. Preclinical and clinical evidence were searched. Overall, drug abusers demonstrated improvements, including better fitness and emotional measures, lower relapse rates, and sustained abstinence when compared to non-exercised individuals. Regarding prevention, the number of studies is scarce and generally of bad quality, namely at the clinical level. In general it could be said that exercise may help to prevent drug addiction with stimulants, like amphetamines, or depressants, like opioids. The neurobiological mechanisms of physical exercise in drug abusers management seem to reflect an interplay of several agents, including neurochemical mediators, oxidative stress, neurogenesis, gliogenesis, and blood-brain barrier dysfunction as disclosed by preclinical data and some clinical results. Exercise-based interventions alone or as an additional therapy may be a useful tool for managing drug addiction.

**Keywords:** exercise, physical activity, drug addiction, drug dependence, amphetamines, opioids

**Resumo**

Esta revisão tem como objetivo descrever o conhecimento atual sobre o exercício físico no tratamento da adicção a drogas de abuso, principalmente na prevenção. Foram utilizados os seguintes termos de pesquisa no PubMed: [“drug addiction” AND “physical exercise” AND “prevention”] ou [“drug addiction prevention” AND “physical exercise]. Referências relevantes de publicações importantes e literatura cinzenta também foram procuradas para identificar citações adicionais para inclusão. Além disso, as referências dos artigos também foram revistas. Foram pesquisada evidências clínicas e pré-clínicas. De um modo geral pode-se afirmar que os utilizadores frequentes de drogas de abuso demonstraram melhorar a sua capacidade ou *fitness*, incluindo melhor aptidão e medidas emocionais, menores taxas de recaída e abstinência sustentada quando comparados com indivíduos que não fazem exercício. No que diz respeito à prevenção, o número de estudos é escasso e geralmente de má qualidade, nomeadamente ao nível clínico. Em geral, pode-se dizer que o exercício pode ajudar a prevenir a adicção com estimulantes, como as anfetaminas, ou depressivos, como os opióides. Os mecanismos neurobiológicos do exercício físico no tratamento da adicção parecem refletir uma interação de vários agentes, incluindo mediadores neuroquímicos, estresse oxidativo, neurogénese, gliogénese e disfunção da barreira hematoencefálica, conforme se deduz dos dados pré-clínicos e de alguns resultados clínicos. As intervenções baseadas no exercício, isoladamente ou como terapia adicional, podem ser uma ferramenta útil para tratar a dependência ou adicção a drogas de abuso.

**Palavras-chave:** exercício físico, atividade física, dependência de drogas, adicção, anfetaminas, opióides

Drug addiction is characterized by a sequence of processes that lead to the relapsing nature of the disorder. Since the dopaminergic mesocorticolimbic system is considered to be involved in reward-related associative learning, reinforcement and incentive salience (Fontes Ribeiro et al., 2011; Morais et al, 2017), it may have a crucial role in the development of drug addiction. For instance, methamphetamine primarily causes the release of the monoamines dopamine (DA), serotonin (5-HT), and norepinephrine (NA). NA is released most efficiently, followed by DA and then 5-HT. On the other hand, physical activity involves the synthesis and release of dopamine in the basal ganglia, including nucleus accumbens, and prefrontal cortex. Therefore, the dopaminergic mesocorticolimbic brain system seems particularly involved in both the execution of physical activity and in some characteristics that may lead to the development of drug addiction. Moreover, there is a widespread recognition that physical activity and exercise (programmed physical activity) are important components of a healthy lifestyle, either in the young or adult age. During early stages of life, physical activity enhances social development and learning (Parcel et al., 1989), whereas later in life, it can help slow the physical and cognitive decline associated with aging (Bardo and Compton, 2015; Cotman and Berchtold, 2007) and protects subjects against many chronic diseases. Thus, physical activity is useful in the prevention and treatment of various diseases, including Alzheimer's disease (Cotman and Berchtold, 2007), obesity-related metabolic diseases (Bardo and Compton, 2015; Bensimhon et al., 2006; Brown and Summerbell, 2009; Qin et al., 2010), such as diabetes mellitus, and psychiatric disorders, such as anxiety and depression (Brown et al., 2013; Holley et al., 2011; Strohle, 2009). The beneficial effects of physical activity on health-related outcomes are thought to be mediated by a wide range of long-term biological alterations, which likely explain the multiple benefits across various disease states. For example, exercise reduces the incidence of obesity-related

diseases, at least in part, by decreasing lipoprotein levels (LDL and principally VLDL) (American College of Sport Medicine, 2018). In contrast, the ability of physical activity to enhance learning during development may be mediated by the proliferation of glial and endothelial cells, as well as an increases in neurogenesis and neuronal connectivity (neuronal plasticity), in brain regions critical for learning and memory (Eckert and Abraham, 2013; Gelfo et al., 2009; Mandyam et al., 2007; Viola et al., 2009). Given the widespread benefits with various disease states, it is appropriate to verify whether physical activity and exercise have utility in the prevention and treatment of substance use disorders, which are the objectives of this review.

## 1. Introduction and objectives

While some success has been achieved in the understanding of the influence of physical activity on drug abuse prevention and treatment (Linke and Ussher, 2015; Lynch et al., 2013; Smith and Lynch, 2011), notable gaps still persist (Bardo and Compton, 2015). In particular, there is little information about the neurobiological mechanisms that specifically mediate the relation between physical activity and drug abuse vulnerability in humans. Further, while exercise-induced changes in reward-relevant neural systems are likely important (Lynch et al., 2013; Morais et al., 2017), there has been little consideration of other neurobehavioral processes such as impulsivity, stress, executive cognitive function, and emotion regulation.

In case of preclinical research, a brief description of key neural mechanisms thought to mediate the effects of physical activity and enrichment on drug reward are presented. While physical activity produces global changes throughout the brain, the medial prefrontal cortex (PFC), limbic system and striatum may play a pivotal role in the relation between physical activity and drug abuse vulnerability. These structures are known to have a role in various addiction-related processes, including reward sensitivity, motivation, inhibitory control, stress reactivity and emotion regulation (Koob et al., 2014; Perry et al., 2011; Rive et al., 2013; Morais et al., 2017).

Taking into account these considerations, the current review highlights a few reports that illustrate the effectiveness of physical activity in treating and, principally, preventing drug use/abuse, translated in drug addiction. However, to perform these objectives we must take into account that some significant barriers have impeded translation of preclinical neurobiological evidence to humans. Moreover, the studies in humans are scarce.

## 2. Methodology

A search in the online database Medline/PubMed was carried out updated until December 2017, using the following search terms [“drug addiction” AND “physical exercise” AND “prevention”] or [“drug addiction prevention” AND “physical exercise”]. The bibliographies of the retrieved articles were searched for additional references. In both Medline/PubMed searches a total of 388 full-text articles were obtained on which inclusion and exclusion criteria were applied. Publications were included if they are: (i) clinical studies evaluating exercise as a therapeutic intervention or prevention for drug addiction, or if (ii) preclinical studies using illicit drug-administration models subjected to physical exercise, and if (iii) papers written in English or Portuguese. Publications were excluded if we cannot find them in full text. Gray literature was also considered, as well as relevant references from key publications obtained from the Medline/PubMed search.

## 3. Physical activity may protect or prevent drug abuse or drug addiction

There has been some success in developing school-, family- and media-based preventive interventions to reduce drug abuse risk among at-risk adolescents and young adults, but these interventions are not fully or widely effective across a range of individuals (Bardo and Compton, 2015). Similarly, for treatment interventions among individuals with substance use disorders, novel medications and immunotherapies for the treatment of substance use disorders have been pursued (Koob et al., 2009; Montoya and Vocci, 2008; Shen and Kosten, 2011), but these medical treatments are not effective across a wide range of individuals and side effect profiles are sometimes problematic. Moreover, a clear or robust demonstration of effectiveness is missing. As discussed below, both preclinical and clinical results may provide evidence that an effective alternative approach is to implement intervention strategies that promote physical activity. This may be accomplished by evaluating physical activity alone or in combination with other preventive and/or treatment modalities.

It is known that there is dependence to exercise (Kerr et al., 2007), namely through the endogenous opioid and serotonergic system. This mechanism may prevent drug abuse through substitution.

### 3.1. Preclinical evidence

At the preclinical level, there is considerable overlap in the protective effects of either physical activity or environmental enrichment on drug use, most likely because exposing animals to enriching stimulation elevates levels of physical activity and reduces body weight (Bardo and Compton, 2015; Bardo and Hammer, 1991; Diamond et al., 1965). For the purpose of this review, however, we focus on physical activity separately,

as enrichment in the absence of physical activity may not induce all of the neurogenic factors responsible for activity-dependent brain adaptations (Bardo and Compton, 2015; Kobilo et al., 2011). However, physical activity without enrichment is not so effective. A host of neural, social and individual difference factors are known to play a role in drug taking behavior. Regardless of the mechanism, however, a consistent finding among the few preclinical studies is that physical activity reduces drug self-administration or drug dependence (Fontes Ribeiro et al., 2011). These findings have been reported across various laboratories and methodologies, as well as across different developmental periods (adolescent and adult) and across both sexes; however, some sex differences exist in the literature, as described previously (Lynch et al., 2013; Zhou et al., 2016), and this may justify different exercise interventions. Increasing evidence has suggested that exercises attenuate drug-seeking behaviors during drug initiation, escalation, extinction, abstinence and relapse.

Animal studies have shown that females have high levels of cell proliferation in the dentate gyrus of the hippocampus, which is mediated by natural fluctuations of gonadal hormones, compared to their male counterpart (Zhou et al., 2016). Moreover, male rats have more dopamine neurons in the substantia nigra, while females have more in the VTA and caudate nucleus (Zhou et al., 2016). Likewise, females have significantly higher levels of dopamine in the PFC, while males have higher levels of dihydroxyphenylacetic acid (dopamine metabolite) (Zhou et al., 2016). This could be related to the fact that dopamine neurotransmission in the female rat is more tightly regulated by autoreceptors and transport in metabolic processes (Zhou et al., 2016). However, the majority of the current studies were not inclusive and were performed on one gender, specifically males.

In both rats and mice, the most common method for promoting physical activity is to provide access to a running wheel, although a treadmill or swimming regimen also have been used, but with less success. In spite of this, principally due to be easier, the treadmill has been used in the majority of studies. The beneficial effect of physical activity is most notable when access to a running wheel occurs during the self-administration session (Cosgrove et al., 2002; Kanarek et al., 1995; Zlebnik et al., 2012, Bardo and Compton, 2015). However, when access to a running wheel is implemented either before or after daily operant conditioning sessions, a decrease in intravenous self-administration is also obtained across different various drugs, including cocaine (Smith et al., 2008b; Smith et al., 2011), methamphetamine (Engelmann et al., 2013; Miller et al., 2012), heroin (Smith and Pitts, 2012) and morphine (Hosseini et al., 2009). Fontes Ribeiro et al (2011) also demonstrated that chronic exercise (8 week treadmill running program, with increasing intensity) decreases the rat preference for a place associated with drug intake (conditioned place preference (CPP) model). Before conditioning none of the animals showed preference for a specific compartment of the apparatus. The used amphetamine dose in the conditioning phase was able to produce a marked preference towards the drug-associated compartment in the group without exercise. In the animals with exercise a significant preference by the compartment associated with saline was observed. In the Institute of Pharmacology and Experimental Therapeutics of the Faculty of Medicine of the University of Coimbra these results have been replicated.

Physical activity also decreases the escalation of self-administration (Engelmann et al., 2013; Zlebniket al., 2012 Bardo and Compton, 2015) and reinstatement (Lynch et al., 2010; Sanchez et al.,2013; Smith et al., 2012; Thanos et al., 2013; Zlebnik et al.,2010; Bardo and Compton, 2015). Smith et al. (2008) found that chronic exercise decreases the positive-reinforcing effects of cocaine and support the possibility that exercise may be an

effective intervention in drug abuse prevention and treatment programs. In the same way, Lynch et al. (2010) demonstrated that the wheel running reduced cocaine-seeking during both extinction and reinstatement. In this work cocaine-seeking was positively associated with pERK levels in the prefrontal cortex, while pERK levels were not different among saline controls. Thus, in the cocaine group pERK levels were significantly decreased by exercise. These authors concluded that aerobic exercise may reduce relapse vulnerability by preventing the increase in cocaine-seeking and associated neuroadaptations in the prefrontal cortex that develop over an abstinence period. Physical activity also decreases reinstatement of nicotine seeking following a period of extinction (Sanchez et al., 2013). Thus, regardless whether applied concomitantly or non-concomitantly with access to drug, engagement in physical activity has a protective effect across different stages of the addiction cycle. Since wheel running alone is rewarding (Rasmussen and Hillman, 2011; Silva and Heyman, 2001; Trost and Hauber, 2014), one potential explanation for the decrease in self-administration is that access to a running wheel serves as an alternative non-drug reinforcer. Physical activity can be viewed as a non-drug substitute, having in common the increase in endogenous opioids and dopamine (Fontes Ribeiro et al., 2011). In fact, in rats, food and sweetened solutions are alternative commodities that can decrease demand for a drug (Comer et al., 1996). Further, when a substitution relationship exists, increasing the value of a non-drug commodity reduces drug choice (Heishman et al., 2000; Stitzer et al., 1983). From a clinical perspective, these latter results suggest that individuals who are inclined to find physical activity to be highly reinforcing may show the greatest reduction in drug self-administration. The dependence to exercise may replace the dependence to drugs. . While one can conclude firmly that physical activity has a protective effect on drug self-administration in laboratory animals, there appears to be at least three important caveats to this conclusion. First, in contrast to stimulant and

opiate self-administration, oral consumption of alcohol is not decreased by access to a running wheel (Crews et al., 2004; Ozburn et al., 2008; Werme et al., 2002), and at least one study found that exercise increases alcohol preference and intake in mice (Werme et al., 2002). While it is not clear what factors account for the difference between alcohol and other drugs of abuse, the route of administration needs to be considered (oral vs. injection), as well as the caloric content of alcohol, which may play a role in intake following physical exertion. Second, in contrast to drug self-administration, the results obtained with conditioned place preference (CPP) are mixed (Bardo and Compton, 2015). Some studies have found that physical activity decreases stimulant and opiate CPP (Chen et al., 2008; Fontes-Ribeiro et al., 2011; Hosseini et al., 2009; Rozeske et al., 2011; Thanos et al., 2010), while others have reported either an increase or no effect (Geuzaine and Tirelli, 2014; Mustroph et al., 2011; Smith et al., 2008a). Perhaps different protocols may explain different results. One notable feature is that all of the mixed results are clustered into studies in the conditioned place preference (CPP) model that have examined cocaine rather than amphetamine, MDMA or morphine. Since cocaine has vasoconstrictive properties not shared by these other drugs, perhaps differential vascular changes induced by the various exercise regimens used across studies may play a role in the lack of consistent findings using cocaine. Third, the beneficial effect of physical activity may not be conferred when exercise is forced, rather than voluntary, during the later stages of the addiction cycle (Lynch et al., 2013). For example, when rats are primed with cocaine following a period of extinction, forced physical activity on a treadmill increases cocaine seeking (Thanos et al., 2013). However, this same study found that forced physical activity decreases cue-induced reinstatement, which indicates the physical activity differentially activates neural systems involved in relapse to either cocaine or cocaine-associated cues. In agreement with this the results obtained in other

animal models may be different: in the forced swimming and treadmill with electrical shocks anxiety must be added.

In the other hand, exercise attenuated drug-induced oxidative stress in brain microvessels by raising antioxidant capacity of these capillaries, and protected against BBB disruption, in mice. This was demonstrated for methamphetamine (Leitão et al., 2018; Toborek et al., 2013).

### 3.2. Clinical evidence

In contrast to preclinical work, one limitation of many clinical studies relates to the cross-sectional designs used for data collection, in general of bad quality. In spite of this, it is known from cross-sectional data that there is an inverse relation between physical activity and smoking behavior in American adolescents (Wilson et al., 2005), which also may happen with drugs of abuse. While this might suggest that interventions that promote physical activity would reduce addiction, there are at least two important shortcomings: First, it is not clear if physical activity precedes or results from a reduction in addiction, or whether the relation exists due to a third factor (e.g., peer affiliation or social interaction). Second, as mentioned previously, since physical activity and smoking are incompatible behaviors, it may be that choosing a physical activity is analogous to choosing an alternative reinforcer to reduce drug use. Such an outcome does not necessarily imply that the relation is mediated by a long-term neurobiological protection. Without inducing long-term neuroadaptive mechanisms that protect against drug abuse vulnerability, any beneficial effects of physical activity might be expected to be transient and thus relatively ineffective in the long-term which oblige to a continuous training or physical activity. In two reviews of the literature by Zschucke et al. (2012) and Bardo and Compton (2015), a few randomized control trials (RCTs) assessing the effects of physical

activity were found to be effective with tobacco smokers attempting to quit; however the clinical evidence was found to be sparse. Since then, several reports have been published to provide a more comprehensive understanding of the effect of physical activity. However, there continues to have a lack of conclusive information from clinical studies (Linke and Ussher, 2015). For the most part, as it was said, evidence for the impact of physical activity on drug intake comes from observational studies, including both cross-sectional and prospective designs. Survey-based research in young subjects demonstrates an association between exercise and drug use, with higher levels of physical activity related to lower use of alcohol, tobacco and marijuana use (Iannotti et al.,2009; Terry-McElrath et al., 2011). Participation in exercise remains associated with lower rates even among those in organized athletics (Terry-McElrath et al., 2011). These findings were extended in a longitudinal study which showed consistently lower substance use during the years ensuing after high school and early adult life when individuals participate in exercise (Terry-McElrath et al., 2011). Small scale studies also have found an association of exercise with improved outcomes for individuals diagnosed with substance use disorders. Some early studies show associations between higher rates of contemporaneous exercise and improved outcomes (Buchowski et al., 2011; Collingwood et al., 1991; Sinyor et al., 1982; Weinstock et al., 2008), and a more recent observational study of marijuana cessation found an association of moderate to high levels of physical activity with lower rates of relapse compared to those with low levels of physical activity (Irons et al., 2014). Further, based on qualitative interviews of former and relapsed heroin users followed up after treatment, approximately one-third of successful abstainers mentioned that exercise was a useful method for facilitating their recovery (Weiss et al., 2014). More important, as the "gold standard" for efficacy evaluation, a number of recent studies have used RCT designs (see Table 2).Unfortunately, treatment studies to date have

shown inconsistent findings about the impact of physical activity on addictions, likely due to some variation in quality across studies (Linke and Ussher, 2015). It is difficult to find randomized controlled trials. In particular, the evidence in preclinical studies on treatment of alcohol abuse has been mixed (Giesen et al., 2015). A recent small scale study found exercise to facilitate recovery among alcohol dependent patients with a sedentary lifestyle (Brown et al., 2014). However, other studies examining the effects of physical activity as a treatment for heavy alcohol use have not yielded positive findings in reducing problematic alcohol use (Kendzor et al., 2008; Weinstock et al., 2014). Therefore these mixed findings parallel the preclinical evidence showing that physical activity does not reliably decrease voluntary alcohol consumption (Crews et al., 2004; Ozburn et al., 2008; Werme et al., 2002a) and they highlight the need for determining the critical conditions under which treatment of alcohol use disorders may benefit from physical activity. With tobacco use, several reports show that exercise improves tobacco cessation treatment outcomes (Bock et al., 1999; Horn et al., 2011; Marcus et al., 1995, 2005; Prochaska et al., 2008). Unfortunately, other clinical trials have yielded no significant benefit as adjunct cessation therapies, perhaps because they were under-powered (Abrantes et al., 2014). This happens with the majority of clinical studies. The apparent beneficial effect on smoking cessation observed in at least some clinical trials may be due to a diminution in cue-induced craving (Van Rensburg et al., 2009), thus reducing the relapse rate. In two recent meta-analyses, it was concluded that the majority of studies support a beneficial effect of physical activity on craving and withdrawal symptoms, at least for a duration of up to 30-min post-exercise (Haasova et al., 2013; Roberts et al., 2012). Because of these promising (though limited) findings, there has been a call for implementing physical activity as an adjunct for smoking cessation, especially among women. However, there is a lack of clarity about the type, duration and

intensity of physical activity that yields the optimal outcome on smoking-related behaviors (Roberts et al., 2012) and other addiction behaviors. The prescription of physical exercise doesn´t have been according to the American College of Sport Medicine (ACSM, 2018), which recommends the FITT-VP scheme (frequency, intensity, time, type – volume, progression). Thus, clinical studies of exercise for tobacco or drugs of abuse use are rare and need larger samples with greater control of intervention parameters. As said before, for drugs other than tobacco and alcohol, studies have been sparse. In other recent studies among methamphetamine dependent individuals treated in either inpatient or outpatient settings, moderate resistance training or treadmill walking/jogging were both shown to improve cardiovascular health within some weeks (Dolezal et al., 2014, 2013), suggesting that different methods for enhancing physical activity can be tailored to different settings during the early treatment phase. No specific improvements in outcomes have been demonstrated in randomized controlled trials (RCTs) using exercise as an in-patient treatment for drugs other than tobacco and alcohol principally due to the lack of good studies and robust methodology. In addition, there also has been little clinical work addressing the specific role for exercise in substance use prevention. If for drug addiction treatment the studies are only a few, for prevention of drug addiction the studies are almost inexistent. This is partly due to the effort and expense required to conduct randomized longitudinal studies in large samples. While drug use as an outcome measure has not been examined thoroughly, the effect of physical activity has been examined for its immediate effects on childhood executive cognitive functioning, which includes processes such as self-regulation and self-control. Given the importance of executive cognitive functioning in predicting later life addictive disorders and multiple social outcomes (Moffitt et al., 2011), studies which document the impact of physical exercise on improved executive functioning in children may be illustrative of the potential impact

of exercise on proximal indicators of drug abuse risk. Two recent studies with pre-adolescent school age children show a modest impact of aerobic exercise on executive functioning, especially for more intense exercise (Davis et al., 2011; Kamijo et al., 2011). However, while exercise may have only a modest direct benefit on executive functioning, the impact may be enhanced by additional interventions such as mindfulness training (Diamond and Lee, 2011), parental modeling (Pentz and Riggs, 2013) or musical training (Hudziak et al., 2014). An afterschool exercise program with 7 to 9 year old children was shown to enhance executive control in a well-designed trial with 221 participants (Hillman et al., 2014). In this study, children were randomized to a wait list control or to the 9 month intervention group who participated in daily moderate to vigorous physical activities designed to improve aerobic fitness. Both groups showed maturation and improvement over the 9 month follow up, but those in the intervention group showed greater improvement in tests of executive function. These results are broadly consistent with earlier trials of using exercise to enhance executive functioning in youth (Chaddock-Heyman et al., 2013; Davis et al., 2011; Kamijo et al., 2011; Krafft et al., 2014). In addition to biologically plausible pathways for exercise's role in reducing drug abuse vulnerability, one must also consider the role for psychosocial mediators such as engagement with pro-social peer groups and exercise as an alternative coping strategy. This is very important in health clubs or centers or associations, where there are more interpersonal interactions. Reduced drug abuse vulnerability may be mediated by improved cognitive functioning which itself can be enhanced with physical exercise (Ploughman, 2008). Physical exercise has been shown to enhance cognitive performance, especially school and reading performance (Etnier et al., 2006; Hillman et al., 2009; Reynolds and Nicolson,2007), which suggests another potential way to reduce drug abuse vulnerability. In addition to enhancing cognitive decision-making, physical activity may

serve as a drug abuse preventive intervention by improving stress reactivity and emotion regulation. While acute exercise activates stress-related systems as measured by cortisol levels, repeated exercise reduces stress reactivity as measured by sympathetic and cardiovascular arousal (Huang et al., 2013). Moreover, exercise-induced increase in endogenous opioids may be a "substitute drug".

In a school setting, high-intensity exercise enhanced salivary cortisol levels compared to watching a movie; however, this effect was obtained in female students only (Budde et al., 2010), perhaps due to methodological issues. In a, observational (cross-sectional) study among adolescent boys and girls, compulsive exercise also was found to be associated with emotion regulation strategies (Goodwin et al., 2012), suggesting that physical activity may promote management of emotion. RCT studies also extensively indicate that physical activity is effective in reducing symptoms of depression and anxiety (Daley, 2008; Bardo and Compton, 2015). Given the co-occurrence of affective disorders, stress-related disorders and substance use disorders, preventive strategies that promote physical activity early in life may be especially beneficial in providing a broad spectrum benefit to overall psychological health. Therefore, it is useful to implement exercise strategies early in life.

## 4. Neural changes mediate the protective effect of physical activity

As discussed previously, one may view physical activity as a rewarding event, at least for the majority of subjects (Azrin et al., 2006; Brene et al., 2007; Bardo and Compton, 2015). It can be considered a positive reinforcing agent, increasing pleasure, or a negative reinforcing agent decreasing the symptoms associated with privation. Thus, in a choice situation when both physical activity and drugs are available concomitantly, physical activity may substitute for drug use. However, evidence indicates that repeated physical activity also produces more enduring neurobehavioral alterations that outlast the choice situation. While multiple neural mechanisms are undoubtedly involved, long-term changes in trophic factors that modulate glial-neuronal interactions controlling neurochemical transmission and stress reactivity may be especially important. In particular, specific changes in limbic and prefrontal brain regions have been identified as mediating the link between physical activity and reduced drug reward. The PFC is an integral part of several key neuro-circuits, including those involved in drug reward, inhibitory control and stress reactivity (Butts et al., 2011; Goeders and Smith, 1983; Koob et al., 2014; Perry et al., 2011; Segovia et al., 2009; Bardo and Compton, 2015). Alterations in these neuro-circuits may mediate, at least in part, the effects of physical activity on drug abuse vulnerability.

In addition exercise promotes neuro-regeneration, as it was demonstrated for amphetamines, for example. In fact, methamphetamine administration in mice decreased expression of tight junction (TJ) proteins and increased blood-brain barrier (BBB) permeability in the hippocampus (Park et al., 2016). These changes were preserved post methamphetamine administration in sedentary mice and were associated with the development of significant aberrations of neural differentiation (Park et al., 2016). Exercise protected against these effects by enhancing the protein expression of TJ

proteins, stabilizing the BBB integrity, enhancing the neural differentiation and protecting against METH-induced systemic increase in inflammatory cytokine levels (Park et al., 2016).

### 4.1. Preclinical evidence

Preclinical evidence indicates that repeated physical activity produces long-term neuroadaptations important in drug abuse vulnerability, although the specific conditions under which either sensitization either sensitization or tolerance occurs remain to be clearly elucidated. With stimulants, repeated running wheel exercise cross-sensitizes to cocaine tested in the CPP model (Bardo and Compton, 2015; Smith et al., 2008a), suggesting that physical activity and stimulant drugs activate a common reward neural circuitry. In the same way, rats given repeated running wheel exercise display cross-tolerance to morphine in the same animal model (CPP) (Lett et al., 2002). Since naloxone blocks the rewarding effect of wheel running (Lett et al.,2001; Vargas-Perez et al., 2008), these results suggest that exercise-induced release of endogenous opioids plays a role in the cross-tolerance to morphine. Importantly, the occurrence of sensitization or tolerance does not simply reflect a difference in the neural mechanisms underlying drug-specific reward mechanisms, as both sensitization and tolerance have been reported across various drugs (Czoty et al., 2010; Lett, 1989; Lorrain et al., 2000; Zerniget al., 2007; Bardo and Compton, 2015). Moreover, within the same study, sensitization or tolerance in dopamine transporter (DAT) function can occur with cocaine self-administration, depending on the temporal pattern of drug intake (Calipari et al., 2013). Thus, for translational research, it will be important to determine what factors are important for producing either cross-tolerance or cross-sensitization between physical activity and drug reward. In the study of Morris et al. (2012), in rats, alterations in the mesolimbic reward pathway were

determined using intracranial self-stimulation following 2 or 5 weeks of running wheel access. Compared to their pre-exercise control levels, wheel running induced a leftward shift in the threshold for self-stimulation, indicating increased sensitivity of the reward pathway. While this outcome might imply greater risk for drug abuse, it is important to point out that animals are thought to regulate their drug intake around some optimal reinforcement or satiation threshold (Lynch and Carroll, 2001; Tsibulsky and Norman, 1999). Perhaps a sensitized mesocorticolimbic reward system following physical activity may lower the reinforcement or satiety threshold, thus leading to reduced intake compared to non-exercised controls. Alternatively, since drug abuse is not simply a problem in reward sensitivity, but also of inhibitory control (Volkow et al., 2011), pre-frontal cortical brain regions involved in inhibitory control may be strengthened by physical activity, thus producing a concomitant decrease in reward sensitivity. Consistent with this latter possibility, running exercise increases brain-derived neurotrophic factor(BDNF) in PFC (Peterson et al., 2014) and blunts the ability of amphetamines, namely 3,4-methylenedioexymethamphetamine (MDMA), to evoke dopamine release in the nucleus accumbens (Chen et al., 2008). It is important to note that drugs 0f abuse, either stimulants or depressants, increase synthesis and release of dopamine in the PFC, limbic system and caudate nucleus (Fontes Ribeiro et al., 2011). Therefore, there is an association of exercise to BDNF to prevent the dysfunctional neuroadaptations induced in PFC and related structures following drug exposure (McGinty et al., 2010). As mentioned previously, PFC is known to be a prominent structure involved in addiction propensity based on its role in reward, stress reactivity, decision-making and inhibitory control (Perry et al., 2011; ). At the cellular level, a host of exercise-induced changes have been identified in reward-, impulsivity- and stress-relevant brain systems. In nucleus accumbens, long-term access to a running wheel increases mRNA for both dopamine D2 and opioid receptors

(Greenwood et al., 2011). Striatal dopamine turnover, dopamine D2 receptor binding and dynorphin mRNA also are increased with running in rats (Gilliam et al., 1984; Hattori et al., 1994; Werme et al., 2000). Consistent with this, in the ventral tegmental area, physical activity increases mRNA for tyrosine hydroxylase (Greenwood et al., 2011), indicating the dopamine signaling to accumbal and prefrontal target regions are enhanced (mesolimbic and mesocortical pathways). In PFC specifically, running wheel activity decreases levels of the phosphorylated extracellular signal-regulated kinase (pERK) and cocaine seeking following a period of abstinence (Lynchet al., 2010). Taken together, these findings suggest that physical activity may mimic some of the cellular effects of chronic drug exposure, thus blunting the relative impact of drugs on these same cellular systems. Despite some of the parallel molecular changes induced by both physical activity and drugs of abuse, the picture is complicated due to differential actions on neurogenesis and gliogenesis. For example, within the hippocampal–prefrontal–amygdala stress axis, repeated exercise training increases bromodeoxyuridine immunoreactivity in hippocampus of rats and mice (Crews et al., 2004; Engelmann et al., 2013; van Praag et al., 1999), indicative of increased neurogenesis. In addition, physical activity enhances proliferation of glial cells in PFC (Mandyam et al., 2007). In contrast to physical activity, however, stimulant drugs cause neuronal and glial death in PFC (Kadota and Kadota, 2004; Kim and Mandyam, 2014; Prudencio et al., 2002) and neuronal cell death in hippocampus. These findings suggest that physical activity may protect against drug-induced cell loss, as well producing neuroadaptive changes in surviving cells that counteract the impact of drug exposure. While the precise mechanisms involved in protecting cell death are not known fully, amphetamine-induced elevations in damaging reactive oxygen species and protein carbonyl levels in hippocampus are prevented by exercise (Segat et al., 2014). More globally, voluntary running wheel activity up-regulates

antioxidative enzymes in whole brain capillaries, which protects against the neurotoxic effects of methamphetamine that occur via a disruption in the blood–brain barrier (Toborek et al., 2013; Leitão et al., 2018). While physical activity may not protect against the initial brain insult to dopaminergic striatal neurons produced by methamphetamine, wheel running accelerates the course of neuronal restoration following damage (O'Dell and Marshall, 2014). Physical activity also restores the loss of dopamine neurons in midbrain periaqueductal gray (PAG) following methamphetamine, as well as reversing the enhancement in methamphetamine reinstatement, which normally accompanies this cell loss (Sobieraj et al., 2014). These latter findings indicate that physical activity may reduce relapse rates following a period of abstinence. Further, since the damaging effects of chronic drug use leads to various cognitive deficits (Gould, 2010; London et al., 2014), physical activity also may be beneficial for ameliorating these cognitive deficits.

### 4.2. Clinical studies

While preclinical evidence implicates cellular and anatomical changes in brain function following physical activity, moving from preclinical to clinical research has been hampered by a lack of information about the potential neural mediators that link physical activity and drug use in humans (Bardo and Compton, 2015). Although modern neuroimaging technologies are available to address this question, these technologies have been used most often by researchers in exercise physiology, rehabilitation, obesity and learning/memory (Boecker et al., 2008a; Tashiro et al., 2008; Vosset al., 2011). A more comprehensive understanding of the drug abuse-related neurobiological adaptations resulting from physical activity will inform researchers and practitioners about the development of improved drug abuse treatment and prevention interventions.

Anatomical work conducted with adults indicates that exercise increases overall brain volume, including white and graymatter (Colcombe et al., 2006). Regional analyses also indicate an increase in hippocampal volume, with no change in caudate nucleus (Erickson et al., 2011), which may be important for the protection of learning and memory processes. In contrast, among young adults (college students), moderate exercise training produces only modest effects on gray/white matter densities compared to non-exercised controls (Gondoh et al.,2009). While these morphometric changes appear modest, near-infrared spectroscopy studies indicate that acute mild exercise increases activation of prefrontal cortical regions (Yanagisawa et al., 2010), indicating that more functional neuroimaging analyses are needed. Some initial clinical work suggests that physical activity may alter neurobiological systems underlying reward-, stress- and emotion-based brain systems. In healthy athletes, positron emission tomography (PET) reveals that strenuous running decreases opioid receptor availability preferentially in prefrontal and limbic brain regions, including prefrontal/orbitofrontal and anterior cingulate cortices, as well as insula and parahippocampal gyrus (Boecker et al., 2008b). However, this same study found that no change in opiate receptor availability in the reward-related nucleus accumbens. Further, healthy adult volunteers exposed to moderate exercise (30 min of treadmill running) show no effect on dopamine receptor availability in caudate nucleus (Wang et al., 2000), a region thought to be important for habit formation. Thus, the effects of physical activity observed in prefrontal and limbic regions may be related more with emotion- and stress-related brain systems than with reward systems per se. Neuroimaging studies have also shown physical activity to affect brain function in alcohol and tobacco using samples. Heavy alcohol drinkers who report high levels of voluntary exercise also show greater integrity of white matter connections involving anterior and dorsal brain regions compared to non-exercising drinkers (Karoly et al., 2013). Among tobacco

dependent smokers, physical activity also decreases cue-induced smoking urge, regardless whether they are undergoing abstinence or not, and this decrease is correlated with fMRI activations of orbitofrontal cortex, caudate nucleus and hippocampal gyrus (Janse Van Rensburg et al., 2009; McClernon et al., 2005). While these studies provide preliminary evidence that physical activity yields functional brain changes useful for treatment of addiction, the evidence is scant for drugs of abuse other than alcohol and tobacco. While little is known about the possible preventive effects of physical activity on illicit drug addiction, evidence indicates that the exercise-induced enhancement of executive cognitive functioning in youth noted previously may involve recruitment of various prefrontal cortical regions (Prakash et al., 2015). In addition, in one correlational study, aerobic fitness in preadolescent children was associated with increased hippocampal volume and memory performance, although no relation to nucleus accumbens volume was found (Chaddock et al., 2010).

If for the preventive role of physical exercise on drug addiction there are only a few studies, regarding the influence of physical activity or exercise in the treatment of drug addiction, there are a lot of work. In general we can say that exercise ameliorates drug addiction. For instance, a meta-analysis of Wang et al. (2014), that included twenty-two studies, found that physical exercise can effectively increase the abstinence rate, ease withdrawal symptoms and reduce anxiety and depression. The physical exercise can more ease the depression symptoms on alcohol and illicit drug abusers than nicotine abusers, and more improve the abstinence rate on illicit drug abusers than the others. Similar treatment effects were found in three categories: exercise intensity, types of exercise, and follow-up periods. But more work is needed.

## 5. Concluding remarks

The key question that this review attempted to answer is whether physical activity prevents drug abuse or addiction. Basic science studies in animal models of drug seeking and drug use risk provide generally strong experimental evidence to conclude that physical activity reduces the acquisition of drug using behavior and facilitates desistence and may prevent drug addiction. Unfortunately, human studies are less clear. Studies of physical activity as a component of drug abuse treatment are suggestive, with the clearest link for tobacco treatment and less for alcohol and illicit drug abuse. Thus, animal models demonstrating that exercise facilitates desistence of drug use are partly supported by the treatment data. Some of the difficulty with the clinical data is due to methodological issues. Imprecise measures of physical activity and characterization of exercise prescription, confounding by participation in exercise without clear details, and rare use of random trial experimental designs (RCT or randomized controlled trials) are among the difficulties and weaknesses in the clinical research to date. The summary is that data are "inconclusive" regarding the salutary impact of physical exercise on drug use onset. Yet, intriguing associations of physical activity with enhanced executive control in children suggests a possible pathway for an important impact. Based on the evidence to date, there are several questions that may be informative for directing both preclinical and clinical future research. While preclinical findings are convincing in demonstrating the effectiveness of physical activity in reducing drug use across the addiction cycle, there is considerable uncertainty about the neurobiological mechanisms that mediate this protective effect. Although a number of cellular, neurochemical and neuroanatomical systems have been identified, particularly in PFC and limbic system, results linking physical activity to decreases in drug use are virtually all correlational. There is no definitive study that demonstrates that any specific neurobiological change is necessary

or sufficient to induce the behavioral change. To answer this question, it will be important to utilize new strategies that manipulate specific mechanisms in the presence and absence of well characterized physical activity in order to determine drug use outcomes. The use of conditional knock-down, knock-in and designer receptors exclusively activated by designed drugs may be helpful in this regard. Moreover, PET and fMRI may help research *in vivo*. However, even these state-of-the-art technologies are limited because it is likely that more than one pathway mediates the relation between physical activity and drug use. With clinical research, not only are there gaps in our neurobiological understanding, there is also uncertainty about what conditions are necessary to translate the strong preclinical evidence into practice. To date, the clinical evidence for showing beneficial effects of physical activity is suggestive but not completely decisive, although the evidence for interventions aimed at smoking cessation are most encouraging. Further research is needed to determine under what conditions and at what stage of development physical activity will be effective as either a prevention or treatment strategy. In this regard, preclinical research is less valuable, because animal models do not adequately address issues such as peer influence and alternative coping strategies as psychosocial mediators. To address further some of the methodological issues in clinical research, biomarkers of strenuous physical activity also are needed to augment the self-report measures generally relied upon. Robust signatures of improved fitness that could be used in population settings would facilitate clinical research and have been the target for research development in some settings. Information about the relationship of physical activity to brain development can help to determine the mechanisms for impact of physical exercise on mental processes such as drug abuse. Given the robust preclinical findings, additional basic and clinical research using novel approaches which address design weaknesses are encouraged.

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