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REVIEW ARTICLE

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The neurobiological mechanisms of physical exercise in methamphetamine addiction

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Abstract

Methamphetamine (METH) is the primary drug within amphetamine-type stimulants which are the second most abused group of drugs worldwide. There is no pharmacological treatment addressed specifically to METH addiction, and behavioral therapy is shadowed by poor long-term recovery and relapse. Therefore, novel approaches to manage METH addiction are an urgent need. This review aims to describe the current state of physical exercise use on methamphetamine addiction management. The following searching terms in PubMed were used: ("physical exercise" OR "exercise") AND "methamphetamine." Relevant references from key publications and gray literature were also reviewed to identify additional citations for inclusion. Original investigation regarding physical exercise and methamphetamine addiction (clinical data) or neurobiological mechanisms of physical exercise in animal models of methamphetamine administration (preclinical data) was included. Overall, METH users demonstrated improvements, including better fitness and emotional measures, lower relapse rates, and sustained abstinence when compared to nonexercised individuals. The neurobiological mechanisms of physical exercise in METH users seem to reflect an interplay of several agents, including neurochemicals, oxidative stress, neurogenesis, gliogenesis, and blood-brain barrier as disclosed by preclinical data. Exercise-based interventions alone or as a conjoint therapy may be a useful tool for managing METH addiction.

KEYWORDS

amphetamine-type stimulants, methamphetamine, methamphetamine addiction, physical exercise

1 | INTRODUCTION

The most recent report from United Nations Office on Drugs and Crime indicates that amphetamine-type stimulants (ATS) are the second most abused group of drugs worldwide.[1] After 3 years of relative stability, ATS seizures reached a new peak of more than 170 tons in 2014.[1] For the past few years, methamphetamine (METH) seizures have accounted for the largest share of global ATS seizures annually (Figure 1), but, although METH is a feature of ATS markets worldwide, it is particularly dominant in East and South-East Asia and North America.[1] It is estimated that 29 million people suffer from drug use disorders, but only 1 in 6 is in treatment.[1] Importantly, the number of people requiring treatment for ATS use is increasing.[1] METH use, in particular, accounts for a large share of people receiving drug treatment in large parts of East and South-East Asia.[1] METH users seeking treatment is also increasing in certain parts of the United States, as well as deaths related to METH misuse[2-4] (Figure 2). Therefore, METH use is a serious worldwide public health problem with major psychiatric and medical consequences, including psychosis, dependence, overdose/death, cognitive, socioeconomic, and legal consequences.[3]

The first two authors contributed equally to this work.

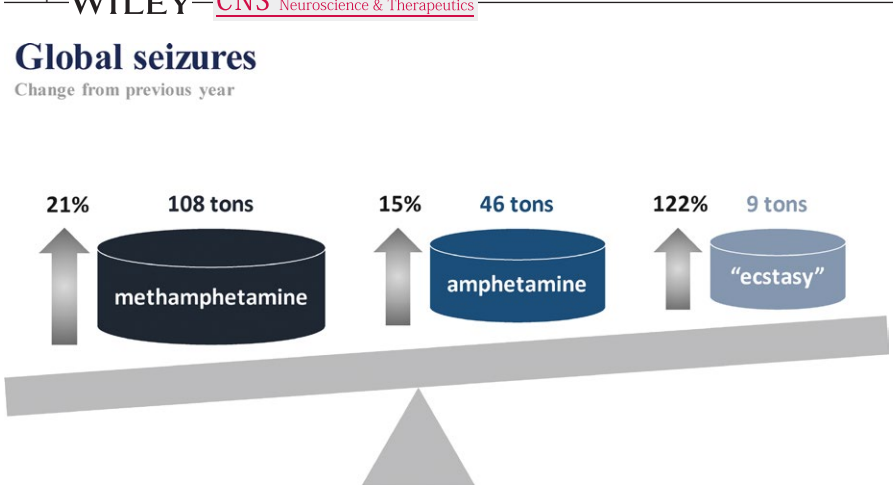


FIGURE 1 Global seizures of ATS including methamphetamine, amphetamine, and "ecstasy" in 2014. This figure was adapted from United Nations Office on Drugs and Crime (UNODC), 2016—World Drug Report 2016

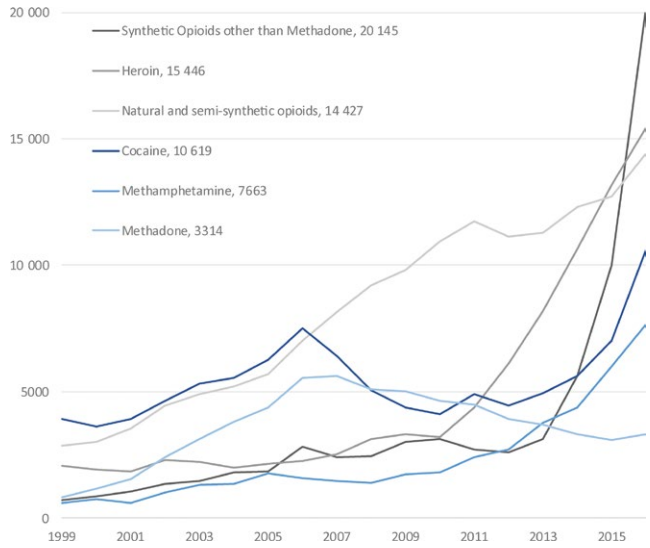


FIGURE 2 Drugs involved in U.S. overdose deaths, 2000-2016. Figure adapted from https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

However, no medication has been approved by the regulatory authorities for the treatment of METH addiction. Finding effective treatment for this clinical problem is certainly an urgent unmet need. The aim of this review was to summarize the evidence of the employment of physical exercise in METH addiction management.

2 | METHODOLOGY

2.1 | Search, information source, and selection studies

A search in the online database PubMed was carried out updated until April 5, 2017, using the following search terms ("methamphetamine") AND (("physical exercise") OR ("exercise")). A total of 101 full-text articles were obtained on which inclusion and exclusion criteria were applied. Publications were included if (i) controlled clinical studies evaluating exercise as a therapeutic intervention for METH addiction were reported or if (ii) preclinical studies using METH-administration models subjected to physical exercise were reported and if (iii) papers were written in English. Publications were excluded if (i) the study design was a review or (ii) METH was used only once or (iii) physical activity was used as a readout of METH neurotoxicity. Twenty studies were included after applying the inclusion and exclusion criteria. Gray literature retrieved from U.S. Department of Justice Drug Enforcement Administration and from United Nations was also considered. Finally, relevant references from key publications obtained from the PubMed search were also included.

3 | METH CLINICAL FEATURES

3.1 | METH pharmacokinetics

METH can be smoked, injected, ingested, dissolved sublingually, or solubilized and when consumed as a liquid, inserted rectally or into the urethra.[3] Smoking (inhaling the fumes after heating the hydrochloride form) is the most common route of administration and has the highest bioavailability following injection (dissolving the hydrochloride form in water prior to injection).[5-7] When smoked or injected intravenously, METH rapidly reaches the cerebral circulation (6-15 seconds), and a rapid onset of euphoria ensues, which typically lasts for several minutes.[8] Therefore, these two routes carry higher potential for acute toxicity, addiction and overdose.[8] Moreover, the risk of infectious diseases, such as human immunodeficiency virus (HIV) and viral hepatitis, through unsafe injecting practices, is noteworthy.[9] In opposition, when "snorted" or ingested in powder form, METH takes approximately 5 and 20 minutes, respectively, to reach a peak of euphoric state.[10] However, this effect can last from 8 to 12 hours.

The metabolism of METH occurs largely in the liver via phase I reactions catalyzed by cytochrome CYP2D6, which produces amphetamine, 4-hydroxymethamphetamine and norephedrine, among other metabolites unlikely to influence the clinical spectrum.[11] Approximately 70% of the drug is then excreted by the kidneys, mainly as nonmetabolized METH (30%-50%), followed by up to 15% as 4-hydroxymethamphetamine and 10% as amphetamine.[7,12]

3.2 | METH toxicodynamics

METH is a cationic lipophilic molecule, being the most potent ATS drug.[13] METH 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.[14,15] A wealth of studies has focused on METH impact on DA release, due to this monoamine's crucial role in reward and reinforcement processes.[11,16] This psychostimulant triggers an aberrant release of DA from the presynaptic terminal into the synaptic cleft as the outcome of the complex interplay of the primary mechanisms of action of METH: the redistribution of DA from synaptic vesicles to the cytosol through the inhibition of vesicular monoamine transporter-2 (VMAT-2) and the reverse transport of DA via DA transporter (DAT).[11,14] METH also competitively inhibits DA uptake and monoamine oxidase.[14,17]

When taken at low-to-moderate doses (5-30 mg), METH induces short-term symptoms that are related with a sympathetic response by the autonomous nervous system (tachycardia, tachypnea, hypertension, pupil dilation, hyperthermia, reduced fatigue) and include a state of euphoria and social ease of relating with other people, increased attention, behavioral disinhibition, reduced appetite, and sense of increased energy, sex drive, and self-confidence.[3,8] Repeated METH abuse results in central nervous system (CNS) disturbances that can range from insomnia, aggression, and mood/anxiety symptoms to severe neuropsychiatric changes.[18] Chronic METH users generally present a decline in cognition associated with impaired episodic memory, executive functions, complex information processing speed, and psychomotor functions[19] that can persist during early[20] and prolonged abstinence.[21] METH users may also present psychosis, comparable to acute episodes of schizophrenia, in which users report delusions, hallucinations, and odd speech.[3,8]

There has been much effort put in elucidating the structural, neurochemical, and metabolic substrate for this well-characterized METH neurotoxicity. Functional neuroimaging studies have documented several alterations in brain activation patterns induced by METH.[22] For example, METH users who showed impaired attention and impaired cognitive control exhibited abnormalities in cingulate gyrus and insula. Additionally, high-resolution MRI and surface-based computational image analyses generated cortical maps that revealed severe gray matter deficits in the cingulate, limbic, and paralimbic cortices of MA abusers, smaller hippocampal volumes than control subjects, and significant white matter hypertrophy.[23] Tobias et al[24] further showed METH abuse produces microstructural abnormalities in white matter underlying and interconnecting prefrontal cortices and hippocampal formation. Furthermore, decreased frontal activation associated with impaired decision making and cognitive control was also disclosed in METH users.[22,25] Maladaptive decision making by METH users may reflect circuit-level dysfunction, underlying deficits in task-based activation: Increased resting-state connectivity within the mesocorticolimbic system coupled with reduced prefrontal cortical connectivity may create a bias toward reward-driven behavior over cognitive control in methamphetamine users.[26]

Additionally, METH abusers have abnormalities in brain regions implicated in mood disorders. In fact, self-reports of depressive symptoms covaried positively with relative glucose metabolism in limbic regions (eg, perigenual anterior cingulate gyrus and amygdala) and ratings of state and trait anxiety covaried negatively with relative activity in the anterior cingulate cortex, orbitofrontal cortex, and left insula, and positively with amygdala activity.[27] Functional magnetic resonance imaging (fMRI) studies disclosed cortical abnormalities that could underlie the socially inappropriate behaviors including violence and aggression often shown by individuals who abuse METH.[28] London et al[29] reviewed clinical studies indicating chronic methamphetamine users often display several signs of corticostriatal dysfunction, including abnormal gray and white matter integrity, monoamine neurotransmitter system deficiencies, neuroinflammation, poor neuronal integrity, and aberrant patterns of brain connectivity and function, both when engaged in cognitive tasks and at rest.

Regarding neurochemical data, clinical studies indicated the presence of a marked monoaminergic dysfunction as reflected by a downregulation of VMAT-2, 5-HT transporter (SERT), DA D2 receptor and DAT in the striatum (nucleus accumbens, caudate and putamen),[21,30,31] and orbitofrontal and dorsolateral prefrontal cortex[32] of METH abusers. It was shown that low striatal D(2)/D(3) receptor availability may mediate impulsive temperament and thereby influence addiction in METH-dependent subjects.[33] Moreover, this low striatal DA receptor availability was linked to caloric intake during abstinence from chronic methamphetamine abuse.[34] Postmortem studies also provided evidence of low levels of DA, tyrosine hydroxylase (TH), and DAT in the striatum[35-37] and SERT in orbitofrontal and occipital cortices.[38]

Oxidative stress is another culprit of METH-induced neurotoxicity. In fact, studies in humans demonstrated that prolonged use of METH exerted oxidative stress and enhanced lipid peroxidation, as METH abusers had significantly higher levels of plasmatic malondialdehyde (MDA, a lipid peroxidation product), when compared to healthy controls.[39] Moreover, METH abusers have persistently higher systemic oxidative stress throughout early abstinence as levered by higher plasmatic levels of MDA, which were accompanied by lower activity of superoxide dismutase (SOD), and higher activity of catalase and levels of glutathione relatively to healthy controls.

New and emergent aspects of METH toxicity involve blood-brain barrier (BBB), neurogenesis, and gliogenesis dysfunction. The majority of evidence regarding BBB disruption is provided by preclinical studies.[40-43] There is scarce human literature corroborating these preclinical evidences. For example, Ago et al[44] reported that a man, who intravenously injected METH, showed brain edema. Additionally, preclinical data suggest that METH can also affect neurogenesis and gliogenesis. For example, Mandyam et al[45] showed that self-administration with daily short or extended access to METH (which mimics a human recreational use) generated a dependence-like syndrome and decreased gliogenesis in medial prefrontal cortex from rats. Mice that were subjected to METH administration for 5 days with an escalating dose regimen showed a reduction in the number of differentiating neural cells in the hippocampal dentate gyrus (DG).[46] In rats self-administering METH for 28 days, the number of proliferating neural progenitor cells

in the hippocampal DGs was significantly increased by METH exposure for 1 hour twice weekly, not changed by daily self-administration for 1 hour, and significantly decreased by daily exposure for 6 hours.[47] Importantly, a robust rebound in neurogenesis was associated with enhanced propensity for reinstatement during METH abstinence in METH self-administered rats.[47] Moreover, forced abstinence from higher preferred levels of METH intake enhanced neurogenesis and neuronal activation of granule cell neurons (GCNs) in the DG and produced compulsive-like drug reinstatement in rats.[48] Furthermore, systemic treatment with the drug isoxazole-9 (a synthetic small molecule known to modulate neurogenesis in the adult rodent brain) during abstinence blocked compulsive-like context-driven methamphetamine reinstatement.[48] These results suggest that adult neurogenesis during abstinence play a role in compulsive-like METH reinstatement.

METH use produces also serious complications in multiple organs, beyond the brain.[49,50] In fact, hyperthermia, hypertension, cardiac arrhythmia, seizures, cerebral hemorrhage, ischemic infarct, renal failure, liver damage, rhabdomyolysis, and wakefulness to the point of collapse and temporary blindness, coma, or death may ensue when METH overdose is in place.[51-55]

Similarly to other drugs of abuse, sudden cessation of METH consumption causes a withdrawal syndrome presenting as anhedonia, irritable or aggressive mood, anxiety, craving, sleep disturbance, diminished cognitive functions, and musculoskeletal pain, among other signs and symptoms, with a prevalence of depressive symptoms.[3,56] This withdrawal syndrome may be a consequence of overall METH neurotoxicity.[11] The neuropsychological consequences of this intricate and complex METH neurotoxicity render management of METH addiction a challenging task.

4 | BIOLOGICAL SEX AND METH ADDICTION

There is scarce information about gender differences in (METH)-dependent users. However, women and men reported regular METH use at a similar age, but, women reported experiencing problems as a result of METH use at an earlier age than men, suggesting a more rapid progression from initial drug use to chronic METH use, and then to problem use.[57,58] A recent epidemiological survey suggested that the proportions of female and male admissions reporting methamphetamine/amphetamines as their primary substance of abuse were similar across all age groups with the exception of those aged 18-24. Specifically, among admissions aged 18-24, 8.9 percent of female admissions reported primary methamphetamine/amphetamine abuse compared with 3.7% of male admissions.[59] Regarding reasons for using METH, women reported "increased energy" and "losing weight", whereas men reported using METH to "complete more work" or to "try something new".[60] A recent study disclosed that METH-dependent women had greater psychological burden, reported more use of an emotional-coping strategy, and had greater childhood emotional and sexual trauma.[61] Kogachi et al[62] investigated the relationships between impulsivity, brain structures, and possible sex-specific differences between METH users and non–drug-using controls. There was no difference in impulsivity between the male and female METH users. However, the female METH users who started using METH at an earlier age had higher impulsivity scores. Contrary to the male METH users, female METH users had smaller and thinner frontal cortices. Moreover, cortical changes in both sexes were associated with greater cognitive impulsivity. These data suggest that sex may modulate the effects of METH on brain morphometry. Overall, the need for gender-tailored METH use treatment programs as suggested by Simpson et al[61] is seemingly warranted.

5 | CURRENT MANAGEMENT AND TREATMENT OF METH ADDICTION

Treatment of METH addiction is a major problem, with elevated overall expenditures due to the requirement of specialized personnel and infrastructures, along with the constant monitoring and follow-up of these patients.[63] Currently, there are limited therapeutic options, with low efficacy and high relapsing rates. Treatment can be directed to acute syndromes or chronic METH abuse. The purpose of this review is to focus on the chronic form of METH addiction.

Methamphetamine user patterns need to be taken into account, when managing METH abusers. Low-, moderate-, and high-use patterns relate with treatment trajectories, as greater treatment participation was achieved when METH use frequency was lower.[64] In addition, individuals who initiated METH consumption at a later age tended to look for treatment at an earlier stage and are less inclined to inject themselves than those who started earlier. Besides, polydrug abuse, often seen on early set use, contributes to low-treatment compliance. An early intervention in all patterns of abuse is essential to decrease METH intake. Gender may also influence treatment outcomes. A follow-up study noticed that, although women were faced with more challenges during treatment, such as unemployment or psychiatric symptoms, compared to men, they were capable of a greater improvement in several areas, including family relationships and medical problems.[57]

In addition, METH withdrawal syndrome is another determinant factor for the treatment process. In fact, the neuropsychiatric impairments (eg, cognitive deficits, depression, and anxiety) that persist following abstinence are associated with poorer treatment outcomes, as follows: increased relapse rates, lower treatment retention rates, and reduced daily functioning.[65] Brecht and Herbeck[66] evaluated the relapsing rates for periods averaging 5 years postdischarge from treatment for METH use. These authors found that, in a sample of 350 subjects, only 13% remained abstinent in the whole 5-year period, and 61% relapsed within the first-year posttreatment, with half the sample relapsing within 6 months. Treatment modality was residential for 62% and outpatient for 38% of METH abusers. Relapsing rates decreased as abstinence period increased. Having experienced serious METH-related psychiatric/behavioral problems and longer duration of treatment worked as protective factors against relapse, while risk factors included having a drug addicted parent and involvement

in METH trade. Initial abstinence should be addressed with supportive measures, such as healthy eating, resting, and exercising, with this one adding a promising new approach.[67] These measures may aid pharmacotherapy, which is mostly unsuccessful, and psychosocial/behavioral treatment, the main, yet flawed, strategy regarding METH dependence.[3]

5.1 | Pharmacotherapy

So far, there is no specific pharmacological treatment for METH addiction.[3,68] Guidelines on this subject regard former and current experience with other stimulant's dependence and they lack proven efficacy studies.[8]

Pharmacological approaches evaluated for METH addiction may interfere with the dopaminergic reward pathways, attenuate negative reinforcing effects of withdrawal, or improve psychiatric symptoms that impair chances of remaining abstinent.[69] This leads to several types of medications that were tested in human laboratory paradigms and in Phase II clinical trials with different outcomes as follows: dexamphetamine, methylphenidate, modafinil (DA indirectly-acting agonists), bupropion, mirtazapine (antidepressants), aripiprazole (antipsychotics), varenicline (nicotinic receptor partial agonist), rivastigmine (cholinesterase inhibitor), perindopril (angiotensin-converting enzyme inhibitor IECA), ibudilast (a phosphodiesterase inhibitor; glial modulator), baclofen, gabapentin (GABAergic agents), topiramate (GABAergic/glutamatergic agent), naltrexone (opioid antagonist), n-acetylcysteine (NAC, antioxidant), ondansetron (5-HT3 receptor antagonist), passive immunization with monoclonal antibodies against METH (ie, vaccines).[69-86] Worley et al[71] highlighted that mirtazapine, bupropion, and methylphenidate have shown some beneficial effect in phase II clinical trials, whereas mirtazapine and bupropion increased METH abstinence, and methylphenidate reduced METH craving and use and improved depressive symptoms. However, the overall efficacy is low. We argue that the physical exercise could augment the efficacy of pharmacotherapy, thus providing a broader and stronger effect in the METH-dependent population. In fact, it was already shown that the combination of PE and sertraline could improve the management of late-life depression, especially when customized for individuals with specific clinical features.[72] The combination of physical exercise and pharmacotherapy in the context of METH addiction needs to be tested in clinical trials.

5.2 | Psychosocial Therapy

Cognitive and behavioral treatments consist essentially in cognitive-behavioral therapy (CBT) and contingency management (CM) and generated good clinical outcomes in METH users.[87] CBT comprises several structure sessions led by a therapist which intends to raise self-awareness to negative actions or particular situations. Although CBT decreases stimulant use, this decrease is not as significant as in CM. The matrix model, a derivative of CBT, was created in the early 1980s to treat cocaine dependence and has suffered several changes since then.[88] Their overall goals consist in the following: interrupting drug abuse, understanding the issues behind relapse and addiction, providing support and education to family members, familiarizing with self-help programs, and monitoring the follow-up status by, for example, collecting urine samples.[63] The program lasts for a preestablished period of 16 weeks and it has, generally, successful outcomes.

Contingency management was originally used in opiate abusers, and it works by strengthening positive behaviors by rewarding the patient, thus leading to sustained abstinence. Rewards include vouchers that can be exchanged for food or any other item or service and even cash incentives. When compared to a counseling-only strategy, CM yielded less positive urine samples and longer periods of abstinence.[67]

Behavioral therapies can be part of a drug court treatment, with the verdict of remain "clean" for at least 1 year and according to a number of norms. Indeed, users who attended drug court treatment fulfilled greater rates of abstinence, retention, and completion.[89] However, Courtney and Ray[3] suggested that caveats must be considered when interpreting conclusions regarding positive outcomes from these psychosocial approaches. For example, the durability of treatment effects (especially with respect to CM programs) was highlighted. Additionally, the effectiveness of psychosocial interventions may be shadowed by poor rates of treatment induction and retention.[90] Furthermore, METH-related cognitive deficits related to inhibitory control may potentially hamper the efficacy of heavily cognitive-based treatments.[3,91]

6 | CLINICAL EVIDENCE FOR PHYSICAL EXERCISE ON METH ADDICTION

Physical exercise has been proposed as a potential treatment for METH addiction. Indeed, exercise was shown to attenuate symptoms of depression and anxiety, prevent addictive behaviors, and improve sleep and cognitive impairments, features often observed in current and former METH users.[92,93] Clinical positive outcomes were observed for several substances, both legal, as tobacco[94] and alcohol,[95] and illegal, as cannabis[96] and heroin.[97]

Newly abstinent METH users submitted to an 8-week endurance training (3 days/week for 3 weeks of jogging and/or walking on a treadmill for 30 minutes at an intensity based on heart rate plus 5 weeks of increasing intensity) followed by a resistance program (progressive, circuit-type program using selectorized machines, and/or dumbbell training that included all the major muscle groups of the upper and lower body) showed substantial improvements in aerobic exercise performance, muscle strength and endurance, body composition, and increased heart rate variability as an index of a healthy autonomic nervous system, which together could enhance recovery from drug dependency.[98,99] However, these authors did not assess endpoints directly associated with METH addiction. Robertson et al[100] aimed to evaluate whether adding an exercise training program to an inpatient behavioral intervention for METH addiction reversed deficits in striatal D2-type receptors. Participants remained abstinent from drugs and received behavioral therapy for their addiction plus 1 h of supervised exercise training, 3 days/week for 8 weeks as implemented by Dolezal et al[98,99] Control participants received equal-time

TABLE 1 Clinical evidence of physical exercise use on methamphetamine addiction management

Reference	Sample	Type of Exercise	Duration of exercise	Outcomes
Dolezal et al[98]	29 METH-dependent individuals finished the proposed program, resulting in a 74% adherence rate; 15 elements in the exercise group and 14 in a health education group without training (sedentary) (n = 39 individuals)	*Aerobic training* (30 min): first 3 wks jogging and/or walking on treadmill during 30 min, at intensity based on heart rate (HR); the subsequent 5 wks had increasing intensity; *Resistance training* (30 min): progressive, circuit-type, resistance training that included all the major muscle groups of the upper and lower body	3 d/wk; 8 wks	Aerobic capacity and endurance: improvement of VO2 max (↑21%) as well as muscle strength and endurance in the exercise group; Body composition and anthropometry: reduction in percent relative body fat (↓15%) and reduction in fat weight (↓18%) in the exercise group.
Dolezal et al[99]	28 METH-dependent individuals under residential treatment were divided into two subgroups of 14 elements: exercise and equal-attention health education program without training (sedentary); these were compared to 22 aged-matched, drug-free, sedentary controls (n = 50, all males)	*Aerobic training* (30 min): first 3 wks jogging and/or walking on treadmill during 30 min, at intensity based on HR; the subsequent 5 wks had increasing intensity; *Resistance training* (30 min): progressive, circuit-type, resistance training that included all the major muscle groups of the upper and lower body	3 d/wk; 8 wks	Exercise markedly increased HRV (HRV was reduced in recently abstinent users when compared with sedentary drug-free controls); Exercise improved gain in aerobic capacity (VO2 max; 24%); Exercise increased muscle strength and endurance for upper (51% and 90%, respectively) and lower body (40% and 112%, respectively) (resistance training); Body composition and anthropometry: reductions in body mass (−3%), percent relative body fat (−14%), and body mass index (−4%) in the exercise group.
Rawson et al[93]	138 METH-dependent individuals under residential treatment were randomly assigned to the exercise group (67 users) or to the Educational group (sedentary; 71 users)	*Aerobic training*: 5 min of warm-up, 30 min of aerobic activity on a treadmill; *Resistance training*: 15 min weight lifting in major muscle groups, and 5 min of cooldown and stretching; 3 d/wk	3 d/wk, 8 wks	8-week follow-up postdischarge: 1 and 2 patients were lost to follow-up from the sedentary and the exercise group, respectively; Physical exercise significantly reduced depression and anxiety symptom scores at study discharge (according to Beck Depression Inventory)
Rawson et al[101]	138 METH-dependent individuals under residential treatment were randomly assigned to the exercise group (71 users) or the educational group (sedentary) (67 users)	*Aerobic training*: 5 min of warm-up, 30 min of aerobic activity on a treadmill; *Resistance training*: 15 min weightlifting in major muscle groups, and 5 min of cooldown and stretching; 3 d/wk	3 d/wk, 8 wks	8-week follow-up postdischarge: 1 and 2 patients were lost to follow-up from the sedentary and the exercise group, respectively; Physical exercise (followed by no additional encouragement or support for continued exercise) decreased METH use among lower severity METH users at 1, 3, and 6 mo posttreatment. This benefit was sustained for 6 mo.
Robertson et al[100]	METH-dependent individuals were randomized to a group that received 1 h supervised exercise training (exercised; n = 10) or one that received equal-time health education training (sedentary; n = 9)	*Aerobic training* (30 min): first 3 wks jogging and/or walking on treadmill during 30 min, at intensity based on HR; the subsequent 5 wks had increasing intensity; *Resistance training* (30 min): progressive, circuit-type, resistance training that included all the major muscle groups of the upper and lower body	3 d/wk; 8 wks	Exercised patients displayed a significant increase in striatal D2/D3 receptor availability compared to the sedentary group; There were no changes in D2/D3 receptor availability in extrastriatal regions in either group.

(Continues)

TABLE 1 (Continued)

Reference	Sample	Type of Exercise	Duration of exercise	Outcomes
Wang et al[103]	Participants were randomly divided into the four treatment groups: the three intensities of exercise treatments (light, moderate, and high) and a reading control	Aerobic exercise: 5-min warm-up; 20-min exercise using a bicycle ergometer at 50 rpm; 5-min cooldown; Participants were instructed to cycle while keeping their HR at one of three desired exercise intensities: within the range of 40%-50%, 65%-75%, or 85%-95% of their maximum HR	Two bouts of acute aerobic exercise 1-week apart	Acute moderate-intensity exercise may be associated with more positive effects related with METH-associated craving and inhibitory control in METH-dependent individuals (behavioral and neuroelectric measures).
Wang et al[105]	Sixty-two people with METH dependencies were recruited through the Drug Rehabilitation Bureau and were assigned to either an aerobic exercise or attentional control group; 50 participants completed the trial.	Aerobic exercise: 5-min warm-up; 30-min sessions of moderate-intensity exercise (ie, cycling, jogging, or jump rope); 5-min cooldown; The exercise training program began at an intensity of 65%-70% of the HR max for each METH-dependent individual. After the second week, the intensity was gradually increased to 70%-75% of HR max, based on the participant's response.	3 d/wk; 12 wks	Moderate-intensity aerobic exercise training attenuated METH-associated cravings and improved inhibitory control in METH-dependent individuals (behavioral and neuroelectric measures).

health education training. D2/D3 receptor availability [measured as nondisplaceable binding potential (BPND)] was monitored by positron emission tomography (PET) using [(18)F]fallypride. Structured exercise training was able to increase striatal D2/D3 receptor availability in comparison to equal time of health education training. These authors suggested further evaluation of physical exercise as an adjunctive treatment for stimulant dependence is warranted.

Other studies also subjected METH-dependent adults to a 8-week period moderate exercise program [5 minutes of warm-up, 30 minutes of aerobic activity on a treadmill (endurance), 15 minutes of resistance training with weightlifting in major muscle groups, and 5 minutes of cooldown and stretching; 3 days/week]. Treadmill speed and resistance weight were progressively increased. The exercised participants showed less depression and anxiety symptoms and returned less to METH use postdischarge, compared to health education participants.[93,101,102] Health education sessions comprised wellness multimedia classes, including nutrition, sleep hygiene, time management, or health screening recommendations. Haglund et al[102] further stressed that participants who attended the greatest number of exercise sessions derived the greatest benefit. Furthermore, exercise appeared to be particularly beneficial to individuals who suffered from severe medical, psychiatric, and addictive disorders.[102]

While physical exercise has shown efficacy in correcting emotional deficits in METH users, METH craving is also a tempting target. Notably, Wang et al[103] expanded Wang et al[104] observations and further showed that acute aerobic exercise (5 minutes warm-up, a 20-minute main exercise on a stationary cycle ergometer at 50 RPMs, and a 5-minute cooldown) may provide benefits for METH-associated cravings and inhibitory control (which is referred as the ability to control inadequate behavior), as revealed by behavioral and neuroelectric measures. Moderate-intensity exercise (heart rate within 65%-75% of the participant's estimated maximum value) may be associated with more positive effects when compared with estimated maximum value and may be associated with more positive effects when compared with light and vigorous intensity. Wang et al[105] extended these observations by demonstrating that aerobic exercise training [a 12-week program: 5-minute warm-up; 30-minute sessions of moderate-intensity exercise (ie, cycling, jogging, or jump rope; heart rate within 65%-75% of the participant's estimated maximum value); 5-minute cooldown] may be also efficacious for METH-associated cravings and inhibitory control among METH-dependent individuals. These authors argued that these evidences may contribute to the development of specific exercise prescriptions for special populations. Table 1 summarizes the clinical studies showing evidence of physical exercise usefulness in managing METH addiction.

Regarding the growing number of studies for the last few years, we argue that exercise-based interventions for managing METH abuse are indeed highly auspicious. Many forms of exercise (eg, running and swimming) may be conducted independently, either at home or outdoors and have the potential to be cost-effective, flexible, and accessible.[106]

However, three cautionary notes should be added. Firstly, there could be various challenges in participant recruitment, enrollment, and

motivation, as highlighted by Brown et al[106] For example, patients having certain medical and psychiatric conditions are generally excluded from the moderate-intensity exercise programs. Moreover, incentives, such as cash, or lack of side effects compared to pharmacotherapy can be used to increase participants' motivation. Secondly, some researchers warn that the advantages of exercise practice are overstated and sport may itself disturb brain function (eg, compromising mental health), especially when intensively performed.[97,107] Thirdly, Lynch et al[108] and Barha et al[109] reviewed clinical as well as preclinical data suggesting that physical activity efficacy may depend upon the following parameters: (i) individuals (ie, by age and sex), (ii) drug classes (ie, alcohol vs nicotine and cocaine), (iii) stage of the addiction process, and (iv) the exercise conditions tested.

Regarding biological sex, it was argued that women benefited more than men in cognitive outcomes.[109] For example, Colcombe and Kramer[110] presented a meta-analysis of 18 RCTs showing that the effect of exercise with an aerobic component on cognition was statistically bigger in samples comprising more than 50% women compared with samples of more than 50% men. Additionally, a 12-month aerobic training resulted in improved attention and memory in older women with MCI, whereas in men, only memory was improved.[111] Finally, Baker et al[112] found that 6 months of high-intensity aerobic exercise had sex bias in cognitive response toward women in the context of mild cognitive impairment. Considering that most of the participants in the studies we reviewed herein were men, it is tempting to speculate that the positive effects of physical exercise would also extend to female METH addicts.

These authors also reviewed METH data, including preclinical studies. For example, Miller et al[113] found that although wheel running (1-hour/day) reduced METH self-administration in rats when it was concurrently available during the acquisition period, it was not effective at decreasing self-administration when it occurred after the acquisition period, indicating that its efficacy may vary with level of exposure or stage of the addiction process. Interestingly, Aarde et al[114] demonstrated that 1-day access to a running wheel at the home cage, prior to self-administration sessions, reduced METH intake in rats. Furthermore, Engelmann et al[115] showed that although access to a running wheel prior to each self-administration session decreased the acquisition of METH self-administration in rats, a history of unlimited access to a wheel without continued availability enhanced rather than attenuated subsequent acquisition. The impact of physical exercise was also assessed in the withdrawal period in animal models. Recently, Damghani et al[116] showed that regular swimming exercise (45 minutes/day, 5 days/week, for 14 days), reduced voluntary METH consumption, and anxiety-like and depression-like behaviors in METH withdrawn rats [rats were exposed to bi-daily doses of METH (2 mg/kg, subcutaneous) over a period of 14 days].

7 | NEUROBIOLOGY OF EXERCISE ON METH ADDICTION MANAGEMENT

The mechanisms of action of physical exercise on the human brain are still poorly known and mostly based on animal studies. Nonetheless, several hypotheses have been proposed to explain the wide variety of beneficial effects attributed to exercise.[108,117]

One possible neurobiological mechanism mediating the effects of exercise is the modulation of CNS neurochemicals, which play a role in drug addiction and are impaired by METH consumption.[108,118] In fact, O'Dell et al[118] showed that when rats engaged in voluntary aerobic exercise (running wheels) for 3 weeks before and 3 weeks after a binge regimen of METH, exercise significantly ameliorated METH-induced decreases in striatal dopaminergic markers including DAT and TH as well as frontoparietal SERT. This animal dopaminergic data correlate with increased striatal D2/D3 receptor availability in exercised METH abstinence. The apparent correction of striatal dopaminergic deficits operated by physical exercise in METH users in both preclinical and clinical settings seemingly offers better treatment outcomes to METH addicts, namely possible correction of the impulsive temperament which is associated with impaired inhibitory control (please see Section METH toxicodynamics). However, prior exercise in running wheels provided no protection against METH-induced damage to striatal DA terminals in male rats.[119] Changes in BDNF levels are also associated to reward-seeking behavior.[120] Hilburn et al[121] newly found that serum BDNF levels in METH-dependent humans were related to the number of abstinent days since last abuse, but not related to craving and substance use history. More recently, Chen et al[122] registered constant low BDNF levels in METH abusers, during early withdrawal, when levels of drug seeking are low, when compared to those of the healthy controls. Voluntary aerobic exercise (wheel running) increases BDNF exon IV transcription in rat hippocampus.[123] However, METH exposure prior to initiation of aerobic exercise (6 weeks of voluntary wheel running) prevented the increases in both cortical and striatal BDNF seen in saline-treated animals that exercised.[120] The impact of physical exercise on BDNF levels in METH addicts warrants further evaluation because it was recently demonstrated that patients with serum BDNF levels ≤1251.0 pg/mL had higher risk of depression symptoms during METH withdrawal.[124] We argue that BDNF modifications may contribute to the mood corrections seen in METH addicts that undergo a physical exercise program.

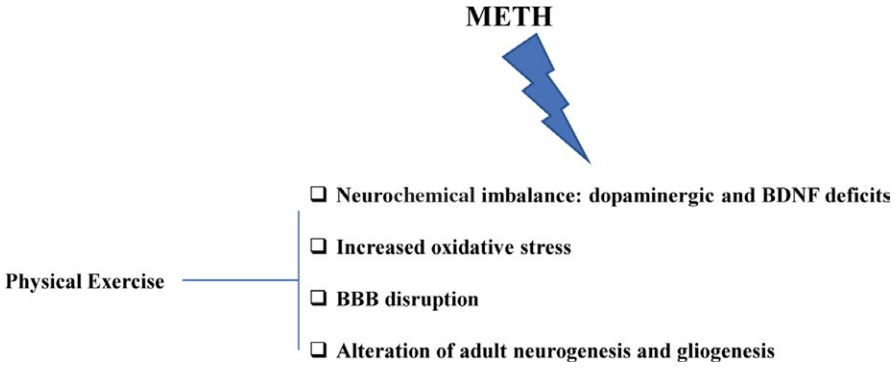
Inoue et al[125] showed that long-term mild (6-week treadmill running training) rather than intense exercise stimulated adult hippocampal neurogenesis in rats, which was correlated with spatial memory improvement. However, there is limited information regarding the effect of exercise on METH-induced neurogenesis impairment. Recently, Sobieraj et al[126] provided immunohistochemical analysis of rat brain tissue demonstrating that wheel running during METH withdrawal did not regulate markers of METH neurotoxicity, including neurogenesis, in brain regions involved in relapse to drug seeking. However, reduced METH seeking was associated with running-induced reduction (and normalization) of the number of TH immunoreactive neurons in the periaqueductal gray (PAG). These authors further suggested that wheel running may be preventing certain allostatic changes in the brain reward and stress systems contributing to the negative reinforcement and perpetuation of the addiction cycle. These authors have previously shown that exercise enhanced medial prefrontal cortex gliogenesis (newly generated astrocytes and oligodendrocytes), which was reduced in METH self-administered rats.[45] On the other

hand, Park et al[46] demonstrated that METH-induced BBB disruption was concurrent with aberrant adult hippocampal neurogenesis in the DG. Importantly, these authors demonstrated that exercise (wheel running activity) that was introduced post-METH exposure in abstinent mice stabilized the BBB and protected against METH-induced alterations in neurogenesis. These authors highlighted the translational value of their work because exercise is frequently being implemented in dependency treatment of substance-abuse patients.[127] Further investigations on the potential role of physical exercise in reversing METH-induced gliogenesis, neurogenesis, and BBB impairment are warranted.

Antioxidant effects have also been observed in individuals who perform regular aerobic exercise.[128] This is consistent with physical exercise ameliorating the reduction-oxidation (redox) balance in the CNS through improvements in the defensive mechanisms of antioxidants.[129,130] Additionally, Speck et al[131] showed that an adequate frequency of moderate-intensity exercise (treadmill) caused antioxidant changes in the hippocampi of mice. Importantly, voluntary exercise attenuated METH-induced oxidative stress in brain microvessels by raising antioxidant capacity of these capillaries, and protected against BBB disruption, in mice.[132] Scheme 1 summarizes the proposed neurobiological mechanisms of physical exercise in methamphetamine users.

8 | CONCLUDING REMARKS

To this date, there is no pharmacological treatment directed specifically to METH dependence; thus, it relies on general drugs used in other dependence treatments and on behavioral therapies, with modest outcomes. Physical exercise has been studied as a conjoint therapy in other substance dependences for some time now, with overall positive feedback on sustained abstinence, as seen with tobacco, alcohol, and cannabis use. Only in the past few years, pertinent clinical studies have been conducted addressing specifically METH. METH users that engaged in a physical exercise program exhibited better fitness measures (which were gauged by substantial improvements in aerobic capacity, muscle strength and endurance, body composition, and increased heart rate variability) and showed less depression and anxiety symptoms, lower relapse rates, and sustained abstinence when compared to nonexercised individuals. The neurobiology of physical exercise in METH users is not fully elucidated and is essentially derived from animal studies. However, positive effects of physical exercise seem to reflect an intricate combination of different players and mechanisms, including neurochemicals, oxidative stress, neurogenesis, gliogenesis, and BBB. Further clinical studies are profoundly needed to confirm reproducibility of previous findings in humans and to dissect the neurobiological basis of physical exercise benefits. We argue that imaging studies (positron emission tomography (PET) and magnetic resonance imaging (MRI) will be instrumental to characterize the impact of PE on oxidative stress (this is a classical METH neurotoxicity hallmark), BBB integrity, and neurogenesis (two recent and exciting hallmarks) in METH addicts.[133-136] Preclinical studies and clinical trials should use physical exercise conjointly with some promising drugs such as mirtazapine, bupropion, and methylphenidate. It is plausible that physical exercise would augment the efficacy of pharmacotherapy. When designing further clinical trials to confirm reproducibility of these beneficial effects of physical exercise on METH addiction, one should attend the following parameters that may help in establishing the most efficient exercise programs: 1—age, 2—sex, 3—neuropsychological consequences of chronic METH use (including cognitive deficits, irritability, agitation, depression, and anxiety symptoms), 4—stage of addiction process (eg, initiation vs relapse), 5—exercise type (anaerobic exercise vs aerobic), duration, and intensity, 5—the need for supervision (structured programs under supervision apparently have better outcomes and most clinical studies happen under residential treatment including psychosocial therapy). As already pinpointed in sections "Biological sex and METH addiction" and "Clinical evidence for physical exercise on METH addiction," men and women may be affected differently by METH use and by physical exercise. Moreover, it was suggested that physical performance decline similarly in men and women at all ages, and the 1-year age-related declines in performance were about twice as great at 40-year-olds than at 20-year-olds.[137] Regarding the stages of the addiction process, exercise typically decreases the reinforcing effects of several drugs of abuse, thus preventing drug use initiation, as was shown for alcohol, cigarette, and marijuana use.[108] Therefore, epidemiological studies evaluating the efficacy of physical exercise in METH initiation are warranted. On the other hand, physical exercise may prevent relapse in METH addicts, as suggested by clinical data reviewed herein. The issue of a structured exercise intervention is seemingly relevant. For example, Brown et al[106] outlined two behavioral axes that accompany a moderate-intensity aerobic exercise:



SCHEME 1 Proposed neurobiological mechanisms of physical exercise in methamphetamine users. Physical exercise reverses the neurochemical imbalance, decreases oxidative stress, stabilizes blood-brain barrier, and corrects alterations in neurogenesis and gliogenesis in METH users

(i) group behavioral training component and (ii) an incentive system. In fact, exercise physiologist and psychologist offered to drug addict cognitive and behavioral techniques aiming to increase overall motivation resulting in improved exercise adherence and maintenance. Moreover, participants earned monetary incentives for various levels of adherence to the exercise program. The ultimate goal was to further increase motivation for participation in the physical activity program across the treatment period. For example, Dolezal et al[98] also referred to a monetary compensation to the METH-dependent individuals in residential treatment during the 12 weeks of study. Regarding exercise type, it has been categorized into aerobic (swimming, running, bicycling) and anaerobic (resistance training, toning) types.[138] While both types singly improve brain function, the combination of the two types of exercise results in markedly better improvements in cognition than aerobic exercise alone.[138] Interestingly, clinical data reviewed herein showed that all physical programs employed a combination of aerobic training (jogging and/or waking on a treadmill and cycling) and resistance training. However, Wang et al[103] used only an aerobic protocol. Nonetheless, it would be interesting to compare the efficacy of both exercise types in the management of METH addicts. Duration and intensity of physical exercise need also to be addressed. In fact, moderate-intensity exercise seems to be associated with more positive effects as highlighted in the Section "Clinical evidence for physical exercise on METH addiction." This is consistent with too much or too little exercise not being advantageous as argued by Alkadhi.[138] Although the exercise programs reviewed in this manuscript had an 8-week duration, it is reasonable to expect that METH users would retrieve sustained benefits should they continue to exercise beyond the scheduled exercise program. Overall, we propose that exercise-based interventions alone or as a conjoint therapy may be a useful tool for managing METH addiction.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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