FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

TRABALHO FINAL DO 6º ANO MÉDICO COM VISTA À ATRIBUIÇÃO DO GRAU DE MESTRE NO ÂMBITO DO CICLO DE ESTUDOS DE MESTRADO INTEGRADO EM MEDICINA

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POSSIBLE ROLE OF EXERCISE ON METHAMPHETAMINE DEPENDENCE MANAGEMENT

ARTIGO DE REVISÃO

ÁREA CIENTÍFICA DE FARMACOLOGIA

TRABALHO REALIZADO SOB A ORIENTAÇÃO DE:
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MARÇO 2015

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Resumo

Cerca de 34,4 milhões de pessoas consumiram estimulantes do tipo anfetamina no último ano avaliado (2012), alertando para a alta prevalência deste grupo, sendo o segundo grupo de drogas mais consumido em vários países a seguir aos canabinóides. A metanfetamina é a droga de eleição neste grupo, sendo usada maioritariamente nos Estados Unidos da América, Norte e Centro da Europa e Sul/Sudeste da Ásia. Deste modo a problemática da dependência de metanfetamina gera grandes encargos sociais, económicos e de saúde pública nestes países. Contudo não há tratamento farmacológico específico e direcionado à dependência de metanfetamina e a evidência neste campo não é abundante comparando a outras drogas de abuso, tendo vindo a crescer recentemente. Nos últimos anos tem havido um maior foco no exercício físico como adjuvante na terapia de doentes dependentes de drogas de abuso, e estudos relativos à metanfetamina têm vindo a crescer em número. O presente trabalho pretende fornecer uma revisão de literatura relativamente ao estado atual do uso de metanfetamina e seu tratamento, e qual o possível papel do exercício físico na terapia destes doentes. Globalmente foram demonstradas melhorias significantes em indivíduos ativos, resultando em melhores parâmetros de capacidade física, baixas taxas de recidiva e abstinência mantida quando comparados a indivíduos que não praticam exercício físico, tanto em estudos com modelos animais como em estudos clínicos. Contudo mais estudos são desesperadamente necessários para confirmar reprodutibilidade destes achados: estabelecer o programa de exercício mais eficaz, atendendo ao sexo, idade e estado mental, nomeadamente em termos de duração, intensidade, tipo e necessidade de supervisão e determinar a associação mais favorável aos tratamentos atualmente disponíveis.

Abstract

An estimated 34,4 million people has consumed amphetamine-type stimulants over the last evaluated year (2012), which alerts for the high prevalence of this drug group, being the second most abused drug group in several countries. Methamphetamine is the primary drug within amphetamine-type stimulants, being highly used in the United States of America, Central and Northern Europe and South/South-eastern Asia. Therefore, methamphetamine use disorder is understandably a major social, economic and healthcare issue among these countries; however there is no pharmacologic treatment addressed specifically to methamphetamine dependence, and overall evidence to specific treatment is not as abundant as with other drugs of abuse. Recently there has been emphasis on physical exercise as a conjoint therapy for drug abuse, and evidence is steadily increasing regarding methamphetamine. The present review pretends to provide an up-to-date overview of the current state of methamphetamine use and evidence on physical exercise and methamphetamine treatment. Overall, there were great improvements demonstrated in users, with better fitness measures, lower relapse rates and sustained abstinence when compared to non-exercised individuals, both in preclinical and clinical studies. However, further studies are profoundly needed, to confirm reproducibility of previous findings and to highlight the following parameters: establish the most efficient exercise program, attending to sex, age and mental consequences of chronic use, namely duration, intensity, type and need of supervision and association with current treatments.

Keywords

Physical exercise; amphetamine; methamphetamine; amphetamine-type stimulants; drug addiction and reward system

Introduction

According to the United Nations Office on Drugs and Crime's (UNODC) "World Drug Report 2014" the market for Amphetamine-type stimulants (ATS) seems to be increasing, with an estimated 34,4 million people (between 0,3 and 1,3 per cent of the world's population) having consumed these substances over the last evaluated year (2012), being the second most widely consumed drug group in many countries right after cannabis, as stated on the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol's 2009 joint publication on methamphetamine. ATS seizures have increased 66 per cent from 2010 to 2011, from 74 tons up to 123 tons, and to 144 tons in 2012 (an increase of 15 per cent), the highest quantity ever noted. The largest slice of the ATS issue corresponds to the methamphetamine (METH) sales market (71 per cent of all seizures), partially due to the rather simple way of manufacturing the drug via clandestine drug labs and the fact that it is a synthetic compound with available chemical substances.

There are two isomers of methamphetamine, which is part of the amphetamine (1-methyl-2-phenylethylamine) type stimulants group: the L- (levorotatory) and the D- (dextrorotatory) forms. The D- form (also called the S- form) is the most biologically active, with the highest capability of stimulating the central nervous system (CNS) and being the widest spread, illicitly available form. METH exerts its effects by various means of action: acting as an indirect agonist, binding itself to dopamine, serotonin and noradrenaline transporters (respectively DAT, SERT and NET) in the cell membrane and also to the vesicular monoamine transporter 2 (VMAT-2). By reversing the function of these transporters, METH manages to release great amounts of monoamines into the cytosol, while also decreasing their metabolism by inhibiting monoamine oxidase (1).

Being such a burden on the worldwide drug control, the management and treatment of METH-dependent users is of great concern in today's clinical practice. Currently the basis of the treatment relies on low-efficacy pharmacologic agents and cognitive-behavioural therapy and contingency management with variable success, as applied to other drug addictions such as alcohol and cocaine addiction. The aim of this review is to provide an up-to-date overview of a recent approach that has been applied to other drug dependencies (i.e. alcohol, cocaine) but only recently began to gain interest regarding methamphetamine use: physical exercise, either aerobic or anaerobic as a support for current treatment.

Methods

Search for up-to-date literature was conducted mainly on PubMed (Medline®) and associated databases, and on the B-on (Biblioteca do Conhecimento Online) online database system of the University of Coimbra, mainly through Reuters's Web of Science™. Publications relevant to the subject were also widely consulted, namely those provided by the United Nations Office on Drug and Crime and European Monitoring Centre for Drugs and Drug Addiction. Preclinical and clinical trials (papers on exercise regimens and its influence on rat models and exercise programs on recovering drug-addicted users) as well as literature reviews on the matter were analysed. Research for literature was initiated on the first quadrimester of 2014. The following main keywords were used: "(physical exercise) and (amphetamine or methamphetamine)", "(physical exercise) and (drug addiction)" and "amphetamine-type stimulants". Additional keywords were vital to the scope of this work: "(exercise) and (drug abuse)", "(methamphetamine) and (exercise)" and "reward system". Relevant references of the searched articles were also included in the overall search criteria.

Results

1. Global Prevalence of Methamphetamine

According to the UNODC, in 2006 there were an estimated 14 million amphetamine users worldwide; in 2012 the best possible estimate is 34 million users (2). In fact, ATS are the second most abused group of drugs in the world after cannabinoids and followed by opioids and opiates, with METH being the main drug within the group. METH consumption and trafficking has been increasing for the last decade. Although, for the last few years the prevalence of METH has remained somewhat stable (figure 1).

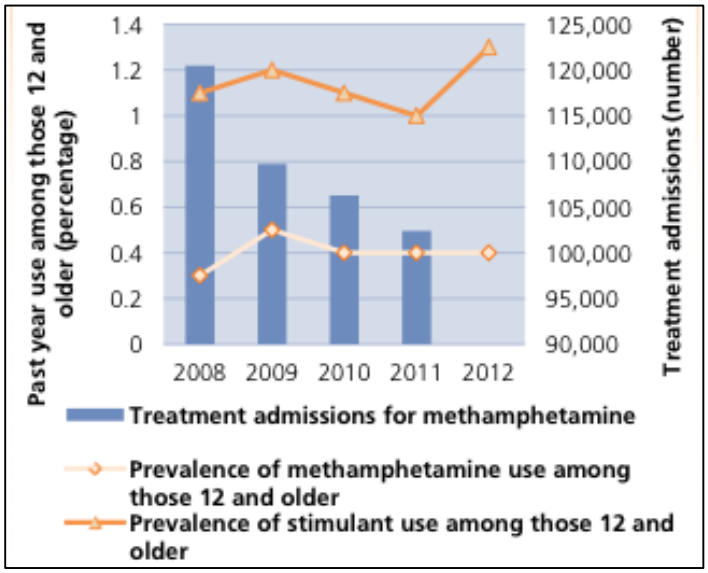

Figure 1: Prevalence of methamphetamine use and treatment admissions for the past few years. Prevalence of METH use remains stable. Adapted from UNODC's World Drug Report 2014 (2).

The same report states that more than 12 571 laboratories were dismantled in 2011, whereas in 2012 this number increased to 14 322. The vast majority of these labs were synthetizing methamphetamine (96 per cent). This tendency also reflects itself on the number of methamphetamine seizures (figure 2): from 24 tons in 2008 to 114 tons in 2012 (from a total of 144 tons).

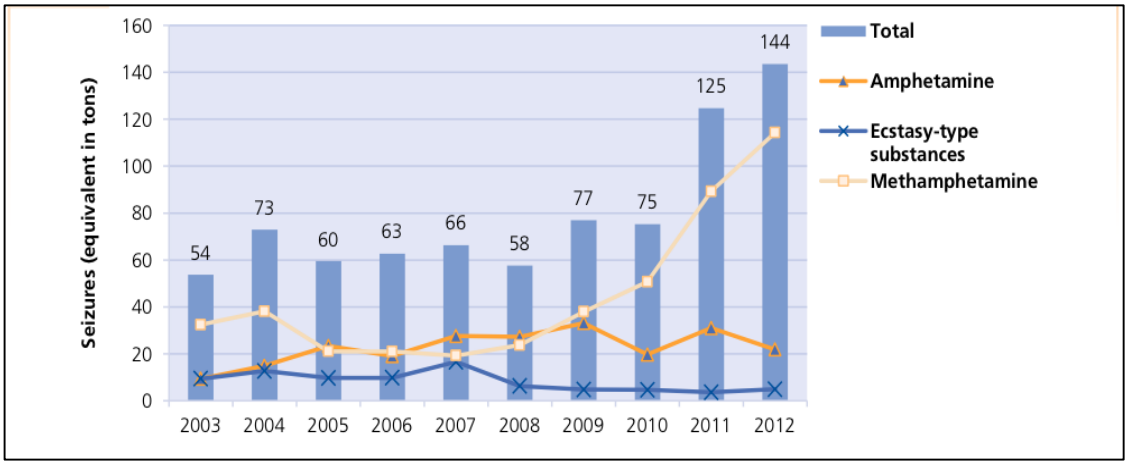

Figure 2: Global seizures of ATS from 2003 to 2012. Methamphetamine, besides being the main drug from the group, shows a rapid growth through the years. Adapted from UNODC's World Drug Report 2014 (2).

By analysing the quantity seized by region, it is clear that North America is the one with the highest amount seized (64 per cent), followed by Eastern and South-eastern Asia (around 33 per cent). By country, the top three consists in Mexico, the United States of America and China, by this order.

This problematic is worsened by an ever-increasing number of organized laboratories, the super labs (built by organized crime societies, such as drug cartels in Mexico) which manufacture the majority of the drug (85 per cent in the United States only), and many small ones, home labs, the so called "Mom and Pop labs", which in turn can be found virtually anywhere, from domestic households, vehicles and garages to hotel rooms, public restrooms and recreational vehicles (3). This can be seen as a public health issue, since the toxic compounds and chemical waste is all in all very hazardous to human health: fumes, vapours and spills due to the manufacture process, drug paraphernalia (pipes, spoons, needles, syringes and masks), contact with the skin leading to severe chemical burns, contaminated objects and inadvertent ingestion. Also, approximately 15 per cent of meth labs are discovered due to explosions and fires, due mainly to careless handling and overheating of the chemical compounds. Intimately associated with household meth labs are poor health conditions, where filth and garbage abound.

Ultimately there are several social issues surrounding an environment where a member of the family or the entire family manages to produce METH, especially when children are involved, as this brings along an array of complications, both physical and psychological, to the normal growth of the child (4).

On a closer note, METH use and addiction in Europe is a lot lower in comparison to North America and Asia. It is the third most consumed synthetic drug after amphetamine and "ecstasy", corresponding to less than 13 per cent of the all ATS seizures (5). Still, it follows the same trend within other regions, as it is slowly expanding during the last decade (6). The best estimates available, as of 2014, point to 2,8 million users in Europe as a whole, with almost 70 per cent represented by Western and Central Europe (1,95 million) (2). Czech Republic and Slovakia present the highest prevalence of METH abuse according to available data, which reveal that demand for treatment is increasing in those countries (61 per cent of all drug treatment patients in Czech Republic report it as the primary drug of abuse whereas in Slovakia it is 26 per cent). Available data is sparse in Europe, with few reports differentiating between amphetamine and methamphetamine in terms of prevalence (figure 3). Although, the EMCDDA 2010 report shows that of a total of 302 kg of METH seized in total only in Europe, the top 6 countries are either Nordic or Central and Baltic countries: Norway (34 per cent), Sweden (25 per cent), Estonia (12 per cent), Latvia (11 per cent), Lithuania (9 per cent), Finland (6 per cent). Czech Republic has a reported high prevalence of METH users and number of labs, but the amount seized corresponds only to 1 per cent of the total.

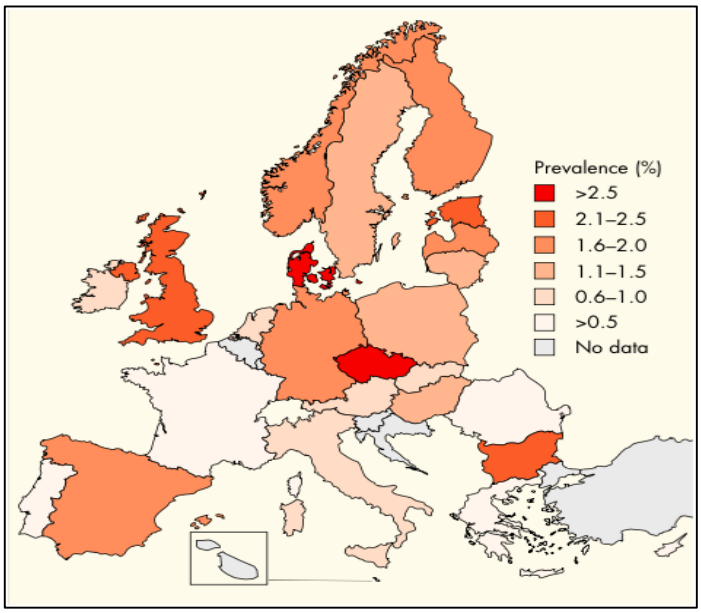

Figure 3: Prevalence of methamphetamine use on young adults (15 to 34 years old). Highest prevalence is mainly found on Central and Northern Europe. Adapted from EMCDDA's Selected Issue 2010 on the Amphetamine and Methamphetamine use in Europe (6).

In Portugal the first dismantlement of a METH lab occurred in 2007, in Viana do Castelo; another piece of news reported a dismantled lab in Terceira Island from the Azores archipelago in 2012 making these the only known METH labs in Portuguese territory so far. The prevalence of amphetamine abuse is rather low (there is no evaluation on METH abuse alone), according to the 3rd National Inquiry on the use of psychoactive substances from 2012 (7): on the general population (from 15 to 64 years old) such lifetime prevalence was 0,5 per cent, increasing to 0,6 per cent in the sub group of 15 to 34 years old. Highest prevalence was noted on Lisbon, Alentejo and Algarve. Altogether, the lifetime prevalence decreased from 2007 to 2012 (0,9 per cent to 0,5 per cent) on the general population, being higher on men. Another study, the ESPAD 2011 (European School Survey Project on Alcohol and other Drugs) shows higher prevalence in the young population, with lifetime prevalence of 3 per cent. Also on this age bracket the Portuguese ECATD 2011 (Study on the Use of Alcohol, Tobacco and Drugs) reports an amphetamine use prevalence between 1.1 to 3.5 per cent.

2. Molecular and Pharmacological Aspects of Methamphetamine

Methamphetamine takes part in a larger group known as "amphetamine-type stimulants" which comprises both "amphetamines" such as amphetamine, methcathinone, fenetylline, ephedrine, pseudoephedrine, methylphenidate and methamphetamine and "ecstasy-type drugs" namely MDMA (3,4-methylenedioxy-methamphetamine) commonly known as "ecstasy", MDA (3,4-methylenedioxyamphetamine) and MDEA (3,4-methylenedioxy-N-ethylamphetamine). The later subgroup is characterized by having hallucinogenic properties (6). Amphetamines are a group of drugs derived from phenylethylamines, with an identical chemical structure to that of dopamine (figure 4). Phenylethylamines are naturally present in the human body acting as a stimulant of the central nervous system, and are synthetized from the amino acid phenylalanine (8). Amphetamines are therefore the methyl derivative of phenylethylamines, sharing the same stimulant properties. METH in turn is the N-methyl derivative of amphetamine, and can exist as one of two isomers: the L- (levorotatory) and D- (dextrorotatory) forms, with D-methamphetamine being the one with highest capacity of stimulating the CNS (up to 3-5 times the activity comparing with the L- form (9)). A popular term for a particular kind of METH is "ice" or "crystal meth", describing the hydrochloride of the D-form (10).

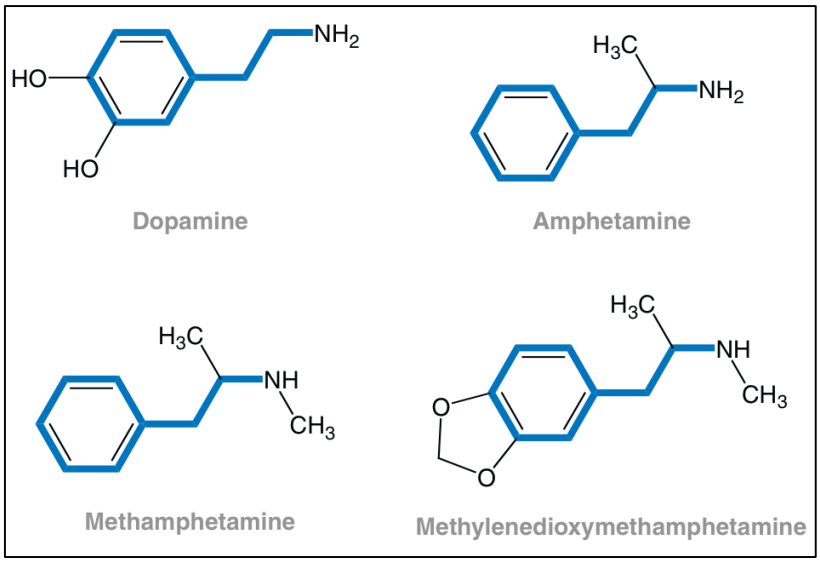

Figure 4: Similarities in the structure of a monoamine (dopamine) and the Amphetamine-type stimulants (amphetamine, methamphetamine and MDMA – "ecstasy"). Adapted from Fleckenstein *et al* (69).

Being a cationic lipophilic molecule, METH is capable of better penetration in the CNS compared to amphetamine, which results in stronger stimulation (11). METH acts as an indirect agonist of dopamine, noradrenaline and serotonin receptors reversing their function and inducing the release of these monoamines and blocking their reuptake in the synaptic cleft (1). Methamphetamine binds to the dopamine transporter (DAT), noradrenaline transporter (NET), serotonin transporter (SERT) and vesicular monoamine transporter-2 (VMAT-2). The final outcome consists in vesicles containing monoamines being emptied into the cytosol thus releasing them into the synaptic cleft and thereby stimulating postsynaptic receptors. In order, norepinephrine and dopamine are more efficiently released than serotonin (12).

To a lesser extent METH also inhibits monoamine oxidase, diminishing their metabolism (10). While VMAT-2, DAT, NET and SERT are integral membrane proteins, the former (VMAT-2) is the only capable of recognizing and transporting all amine neurotransmitters, while the others are selective for the respective amine. Also, VMAT-2 is part of vesicular membranes, while the others are plasma membrane transporters; its function is to transport and store monoamine

neurotransmitters (dopamine, noradrenaline and serotonin) in vesicles within the neurons to be posteriorly released onto the synaptic cleft (12).

The selective transporters retrieve monoamine neurotransmitters from the synapse into the neuronal cytosol, attenuating their action in the postsynaptic receptors. METH seems to take effect mainly on the dopaminergic system; therefore, by stimulating the release of dopamine into the synapse, METH acts on the major CNS dopaminergic circuitry: the mesolimbic, mesocortical and the nigrostriatal pathways, which take a huge part on the dependency pathways for drug abusers (1,13). Each one is responsible for specific actions and reactions of the individual, as described in the comprehensive review by Hsieh, Stein and Howells (14): mesolimbic circuit acts in reward processing, effort related functions and translation of emotions into actions; mesocortical circuit intervenes in cognitive functions namely working memory and the nigrostriatal pathway is involved in the control of expression and direction of behaviour to predictable stimulus or reward. Positive reinforcing effects stem from the activation of the ventral tegmental area of the midbrain dopamine system and the prefrontal cortex and limbic regions (including the nucleus accumbens), which in turn are capable of inducing addictive habits (9).

3. Methamphetamine: Clinical Pharmacokinetics, Pharmacodynamics and Toxicodynamics

Being a synthetic drug, METH can be produced by using various chemical compounds and "cooking" them (the street term for the process of manufacturing METH). A myriad of names can be used to describe METH on the streets and illegal market: speed, crank, meth, crystal meth, ice (in the U.S.A.), Pervitin (Czech Republic), yaba and shabu (Far East). There is a myriad of routes of administration; according to the National Institute on Drug Abuse, the most common method is by smoking (inhaling the fumes after heating the hydrochloride form) providing a quick absorption and access to the CNS where it will exert its effects. This route of administration has the highest bioavailability following injecting. Despite of smoking being the most common, method of use varies by region. There are several other ways of consumption, either by dissolving the hydrochloride form in water and thus injecting it or by "snorting" and ingesting methamphetamine in powder form, where it is absorbed by the mucous membranes, including rectally and sublingually (8).

METH is extensively metabolized in the liver via phase I reactions mediated by cytochrome p450 2D6 (1,10): N-demethylation produces amphetamine; aromatic hydroxylation produces 4-hydroxymethamphetamine and finally β-hydroxylation produces norephedrine, among other metabolites (e.g. hippuric acid) that have little influence on the clinical spectrum. Regarding phase II reactions, N-acetylation and other conjugation reactions occur. Afterwards the kidneys eliminate some 30 to 50 per cent as non-metabolized METH, while the rest corresponds to the various metabolites, and the kidneys eliminate 70 per cent of a single oral dose during the first 24 hours.

Being a stimulant drug of the CNS, methamphetamine shares its effects with other stimulant drugs, both inside the group of ATS and out (such as cocaine). The clinical presentation is

dominated by signs and symptoms translating a sympathetic response by the autonomous nervous system (tachycardia, tachypnea, hypertension, pupil dilation, hyperthermia, reduced fatigue) and by a state of euphoria and social ease of relating with other people, increased attention, behavioural disinhibition, reduced appetite, and sense of increased energy, sex drive and self-confidence (10,15). Repeated abuse of methamphetamine (sometimes every few hours - called "binging", also when referring to other substances, as alcohol) results in mental disturbance, from insomnia, an aggressive state and depressive mood to severe psychiatric conditions such as methamphetamine-induced psychosis, comparable to acute episodes of schizophrenia, where users relate delusions (persecutory, reference, mind-reading), hallucinations (mainly auditory, also visual and tactile) and odd speech (1,10). Understandably, METH can lead to serious cardiovascular (e.g. arrhythmia, acute coronary syndrome, sudden cardiac death and aortic dissection) and systemic conditions (e.g. bruxism, tremor) such as the so-called "meth mouth", with severe teeth decay (16).

As with other drugs of abuse, sudden cessation of methamphetamine causes a withdrawal syndrome presenting as anhedonia, irritable or aggressive mood, sleep disturbance, diminished cognitive functions, anxiety and craving and musculoskeletal pain among other signs and symptoms, with depressive symptoms being characteristic of this drug's withdrawal syndrome (10,17). This may be caused by depleted monoamine reserves which were storing monoamines before beginning of abuse, down regulation of receptors and overall neurotoxicity (1). In fact, long-lasting abuse of amphetamines leads to down-regulation of D_1 (expressed in the striatonigral neurons) and D_2 (expressed in striatopallidal neurons) dopamine receptors causing an imbalance of this neurotransmitter as observed in several studies before (18). METH users have reduced dopamine and serotonin axonal markers, decreased striatal dopamine transporter density and damaged dopamine nerve terminals. The levels of various metabolites related with neuronal viability are decreased, due to neurotoxicity, namely n-acetyl-aspartate and ratio of

this metabolite to creatine. On the other hand, concentration of choline metabolites is higher in frontal regions and in the basal ganglia (19). Dopaminergic terminals located in the ventrolateral caudate nucleus and putamen are the most damaged, while those located in the dorsolateral caudate nucleus and putamen are the least harmed, and those located in the nucleus accumbens are mostly spared (20). Additionally, neuronal lesion takes place primarily in the axonal and terminal (telodendria) parts; although the precise mechanism of toxicity has not been completely understood. However a possible mechanism is oxidation of dopamine and serotonin into 6-hydroxydopamine and 5,6-dihydroxytryptamine, which in turn can oxidize proteins, nucleic acids and lipids in neurons where these neurotransmitters abound (1). Amphetamine causes the build-up of dopamine, which when in excess is then prone to oxidation and originates dopamine-quinones therefore damaging macromolecules (21). There is also evidence of lower perfusion to the brain tissue and decreased levels of SERT in cortical and subcortical (including the striatum – caudate nucleus and putamen), DAT and VMAT-2 in the striatum in abstinence users (14,19).

Glial cells are also damaged in METH use disorder. For example, it was demonstrated that daily methamphetamine use decreases oligodendrocytes and astrocytes in the prefrontal cortex of laboratory rats as a consequence of a decrease in gliogenesis; this reduction was associated with methamphetamine intake (22). However, METH acutely increased gliogenesis in prefrontal cortex (22). Regarding brain structural changes, METH users seem to have smaller grey-matter volume on the cortex (frontal, occipital, temporal and insular lobes) but larger on the striatum; following 3 to 4 months of abstinence, grey-matter volume is higher in several regions of the CNS (parietal cortex, caudate nucleus, nucleus accumbens and lenticular nucleus - putamen and globus pallidus) than in non-users (19).

These cellular, neurochemical and structural changes might translate into neurological and psychiatric changes. In fact, chronic methamphetamine users show a decline at a cognitive

level, with impaired episodic memory, executive functions (such as problem solving), complex information processing speed and psychomotor functions; this impairment is potentially reversed with sustained abstinence (10,19). These cognitive findings are rather relevant, as the cognitive assessment is a phenomenal aid when choosing optimal treatment for each case, so much so that users with impaired cognitive functions are less prone to maintain a sustained treatment and become less engaged in the process (18).

4. Addiction and Reward

Early theories to explain addiction reside in reinforcement principles and conditioning, namely positive reinforcement, ultimately leading to repeated use of a substance and negative reinforcement, as observed with the withdrawal syndrome. Each drug class activates specific receptors or acts in a specific way, often sharing their effects in the CNS as seen with amphetamines and cocaine for instance, both acting in monoamine transporters and their concentration in the synapse. Regarding psychostimulants, their action in the DAT by inhibiting the dopamine reuptake in the nucleus accumbens seems to be the main mechanism responsible for positive reinforcement seen in these users (23). Physical exercise acts in several of the same pathways that constitute addiction and reward neurobiology, as posteriorly developed.

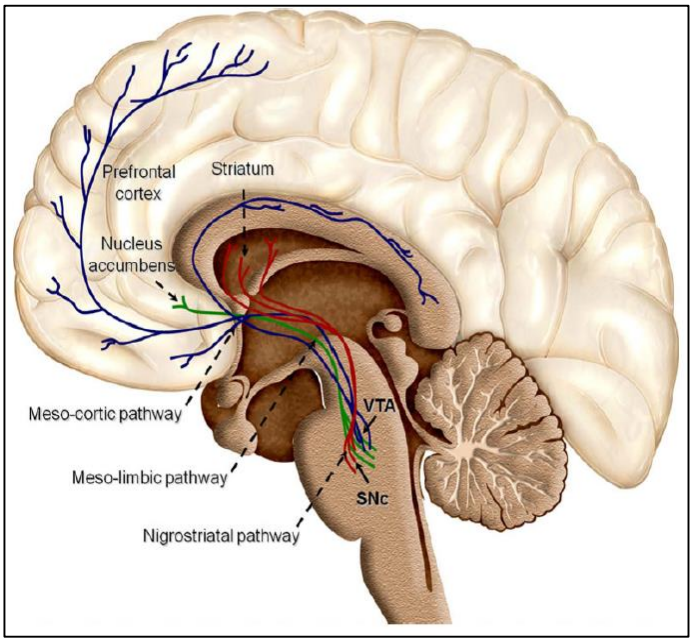

Figure 5: The dopaminergic system. Dopaminergic neurons from the mesencephalon head to cortices (specially, prefrontal cortex) (blue), the nucleus accumbens (green) and the striatum (red). VTA: ventral tegmental area; SNc: substantia nigra pars compacta. Adapted from Arias-Carrión O *et al* (25)

As briefly described earlier, the mesocorticolimbic and nigrostriatal system are deeply involved in reward and consequently addiction (24). Dopaminergic pathways encompass the following routes: from the ventral tegmental area (VTA) of the midbrain to the limbic system, primarily

to the nucleus accumbens (mesolimbic); from the VTA to the cortices, namely the prefrontal, cingulate and perirhinal (mesocortical) and from the pars compacta of the substantia nigra (nigrostriatal), as summarized in figure 5. Besides reward, these dopaminergic pathways play a predominant role on craving and relapse. These neurons have several types of dopamine receptors, grouped in two families, the D1-like receptors, comprising D1 and D5 (which activate the enzyme adenylyl cyclase) and the D2-like receptors, namely D2, D3 and D4 receptors (which in turn inhibit this enzyme). D1-like receptors are mainly found in the prefrontal cortex, while D2-like receptors are mostly found in the striatum and nucleus accumbens (25). Other mechanisms and neurotransmitters also take a part on the reinforcement effects of drug addiction: GABA, opioid peptides (such as endorphins) and glutamate all contribute to this process (figure 6).

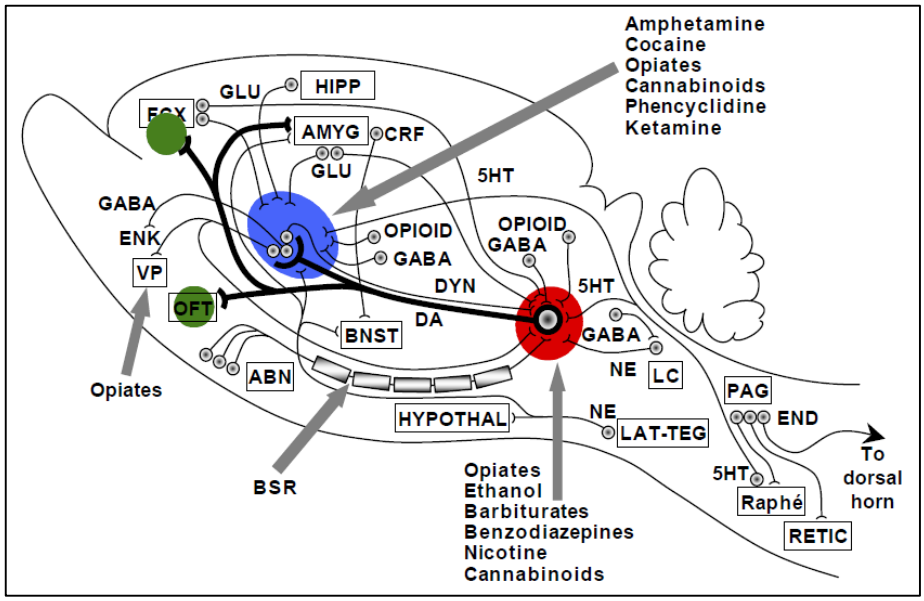

Figure 6: Reward pathways in the brain of the laboratory rat and sites of drug action. Dopaminergic, GABAergic, glutamatergic and opioid circuits are shown.

Blue area: nucleus accumbens; Red area: ventral tegmental area; Green area: frontal cortex (FCX) and olfactory tubercle (OFT); ABN: anterior bed nuclei of the medial forebrain bundle; AMYG: amygdala; BNST: bed nucleus of the stria terminalis; BSR: brain-stimulation reward; CRF: corticotropin releasing factor; DA: dopamine; DYN: dynorphin; END: endorphin; ENK: enkephalin; GABA: gamma-aminobutyric acid; GLU: glutamate; HIPP: hippocampus; 5HT: serotonin; HYPOTHAL: hypothalamus; LAT-TEG: lateral tegmental noradrenergic cell groups; LC: locus coeruleus; NE: norepinephrine; OPIOID: opioid peptides; PAG: periaqueductal grey matter; Raphe: raphe nuclei; RETIC: reticular formation of the brain stem; VP: ventral pallidum. Adapted from Gardner E. L. (67)

5. Current Management and Treatment of Acute Use

Up until now, there are limited options for the treatment of methamphetamine use disorder, with low efficacy and high relapsing rates. Stimulant use disorder (where methamphetamine abuse is included), as defined by the DSM-5 (figure 7) consists in several items which are put together to translate a mild, moderate or severe abuse (the term *abuse* was exchanged for the less demeaning word *use* on the new edition). Treatment can be directed to acute syndromes and chronic use/dependence. The purpose of this review is to focus on the chronic form of METH use disorder; therefore acute treatment will only be reviewed briefly. In many ways methamphetamine-related diseases are treated the same way as other causes (for instance cardiovascular consequences) despite the increasing number of emergency room visits (26). Acute intoxication can be managed using supportive measures most of the times (according to severity of the patient's state of presentation), either by "talking down", where the doctor calms down the patient by talking to him in a quiet environment or by taking a more direct approach using sedatives, namely an anxiolytic (benzodiazepine) or a strong antipsychotic drug when facing aggressive or paranoid patients. Drugs of choice should be midazolam, a benzodiazepine with higher sedative than anxiolytic power or other drug from the same group (such as lorazepam or diazepam) and haloperidol or droperidol (both butyrophenones), as there are no significant differences in need for repeat of sedation and adverse effects between the two (27). Newer atypical antipsychotics can also be used instead of haloperidol, namely olanzapine and ziprasidone (26).

A. A pattern of amphetamine-type substance, cocaine, or other stimulant use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. The stimulant is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control stimulant use.
3. A great deal of time is spent in activities necessary to obtain the stimulant, use the stimulant, or recover from its effects.
4. Craving, or a strong desire or urge to use the stimulant.
5. Recurrent stimulant use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued stimulant use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the stimulant.
7. Important social, occupational, or recreational activities are given up or reduced because of stimulant use.
8. Recurrent stimulant use in situations in which it is physically hazardous.
9. Stimulant use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the stimulant.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of the stimulant to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of the stimulant.

    Note: This criterion is not considered to be met for those taking stimulant medications solely under appropriate medical supervision, such as medications for attention-deficit/hyperactivity disorder or narcolepsy.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for the stimulant (refer to Criteria A and B of the criteria set for stimulant withdrawal, p. 569).
    b. The stimulant (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

Figure 7: Diagnostic criteria for stimulant use disorder.

Mild: 2 to 3 symptoms. Moderate: 4 to 5 symptoms. Severe: ≥ 6 symptoms.

Adapted from Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (70).

6. Methamphetamine Dependence Management

6.1 General Considerations

There are rather aggravating problems concerning the treatment of METH use disorder. The overall costs are too high in some aspects, as the need of specialized personnel and infrastructures, along with the necessity of a continued monitoring and follow-up of these patients, as a short-term strategy is not usually ideal (28).

Significant differences between user groups need to be taken into account: users who initiate drug use later tend to start treatment before earlier users and are also less inclined to inject METH; simultaneous abuse of other drugs also contributes to low-treatment compliance and is seen mainly on early onset use, which demand particular care (29). The authors of this same study state that probably a high level of treatment early on is essential to decrease use in moderate to heavy users, and overall treatment should be started as early as possible with positive outcomes. Gender also plays a determinant role in drug abuse. A study by Hser *et al* noticed that in a population of 1073 METH abusers (both men and women) from California women had more severe issues, as unemployment and mental diseases than men, ultimately leading to serious challenges during treatment, despite showing greater improvement (30).

Aggravatingly, amphetamine's withdrawal syndrome is a predominant factor to take into consideration, usually happening within 24 hours of sudden cessation of drug use (31). As described before, it consists in severe depressive symptoms, such as long-lasting anhedonia, dysphoria and craving (28). Methamphetamine dependence is associated with high rates of relapse, contributing to the difficulty of the treatment. A recent study by Brecht and Herbeck (32) tried to shine a light on long term (5 years) abstinence and relapse rates for METH abusers. The researchers found that out of a sample of 350 subjects only 13 per cent maintained abstinence in this 5-year period, and 61 per cent relapsed during the first year after treatment.

This is highly significant, as early rates of relapse, as seen with other drugs of abuse, are usually related to an increased effort of maintaining abstinence afterwards. Although, relapse rates decrease as abstinence period increases. The authors also identify two main risks of earlier relapse: individuals whose parents used drugs before and dealing with METH sales. Initial abstinence should be addressed with supportive measures, as Ling *et al* report (26): healthy eating, resting and exercising, with the latter being a promising new approach. These supportive measures are subsidiary to pharmacotherapy and to psychosocial and behavioural treatment. One should stress that while pharmacotherapy is essentially unsatisfactory, the latter is currently the primary strategy regarding METH dependence (33).

6.2 Pharmacotherapy

So far, there is no adequate pharmacological treatment specifically for methamphetamine dependence (9,10). Guidelines on the subject take into account past and current experience with other stimulant's dependence, and often there is plainly a shortage of proven efficacy studies (15). Although, it is noticeable that emphasis on the area is increasing, with more studies being developed (34). Pharmacotherapy revolves around the monoamine transporters and mechanisms behind their release and reuptake on the synapse, with the goal of re-establishing depleted storage vesicles in the CNS and improving dysregulation of the physiologic monoamine system. Therefore, the primary aim is to intervene in the dopaminergic reward pathways, act in the negative reinforcing effects of withdrawal syndrome and improve psychiatric consequences of chronic abuse that impair chances of maintaining abstinence (35). There is indeed evidence supporting the usefulness of drugs that release both dopamine and serotonin in stimulant abuse dependence (12). This leads to several drug classes that can and are used with variable results, as thorough reviews on the subject inform (34,35): dopamine agonists (e.g. methylphenidate, modafinil), antidepressants (bupropion, selective serotonin

reuptake inhibitors), antipsychotics (both first and second generation, by antagonism of D_2 receptors), 5-hidroxytriptamine type 3 receptor antagonists (ondansetron), GABAergic agents (e.g. baclofen, gabapentine) and eventually cholinesterase inhibitors (rivastigmine). There are new strategies being taken in consideration and new drugs under development. M. Brensilver *et al* (35) mention a phosphodiesterase inhibitor used for a long time for the asthma treatment in Japan with anti-inflammatory properties discovered in recent years, decreasing METH-induced glial cell activation. Mirtazapine is another promising new option under investigation; cholinergic mechanisms are also being addressed, despite the current lack of evidence in this particular area. On the other hand, L. Karila *et al* (34) bring even more new approaches to the table: monoclonal antibodies against methamphetamine, immunization therapies (i.e. vaccines), involvement of the endogenous cannabinoid system, agonists of nicotinic receptors and drugs from the family of benzoquinolizines. Newly discovered dopamine receptors, namely D_3 could possibly be an effective therapeutic target in METH dependence (36).

6.3 Behavioural Therapy

Being a highly addictive stimulant, methamphetamine dependence can be extremely challenging to treat, both to the user as to the healthcare professional (28). A conjoint strategy of available therapies seems to work better than a stand-alone one. Apparently, treatment responses of METH users are overlapping with those of cocaine users (37). There are essentially two behavioural treatment options (26): cognitive-behavioural therapy (CBT) and contingency management (CM). CBT comprises several structured sessions led by a therapist pretending to raise self-awareness to negative actions or particular situations. It is proven to have decreased stimulant use; however, when compared to CM, this decrease is not as significant. A derivate of CBT is the Matrix model, initially developed to treat cocaine dependence (38). Created in the early 1980's, it has suffered various changes according to increasing evidence since then.

As with CBT, the therapist with specialized training is the main agent in the whole program, establishing a relationship with the patient which serves as a foundation to elicit positive actions and behaviour. The main objectives are to interrupt drug use; understand the issues behind relapse and addiction; provide support and educate family members; familiarize with self-help programs and provide some type of follow-up, as with urine samples (28). The program lasts for a pre-established period of time, originally 16 weeks. There is also proof of significant results on follow-up with this model.

CM in turn began with opiate abusers, and works by strengthening positive behaviours by rewarding the patient, thus leading to sustained abstinence. Rewards include vouchers (which can be exchanged for food or any other item or service) or even cash incentives. When compared to a counselling-only strategy, CM provided less positive urine samples and longer periods of abstinence (26).

Behavioural strategies can be associated to drug court treatment, where the individual is requested to remain "clean" for a period of time (no less than one year) and according to a number of norms. A recent study concluded that users who attended drug court treatment shown higher abstinence, completion and retention rates (39).

7. Physical Exercise as a Conjoint Therapy

The advantages of physical exercise are widely described; there is robust evidence of benefit specifically to the CNS (40). Drug abusers seem to be generally sedentary or low active individuals with little aerobic capacity (maximum quantity of consumed oxygen by the individual during intense exercise, per time unit) (41). Positive outcome has already been evaluated for several substances, both legal, as tobacco (42) and alcohol (43) and illegal, as cocaine (44), cannabis (45) and MDMA (46).

Evidence supporting the role of physical exercise on amphetamine and methamphetamine dependence is steadily rising. A recent paper by Smith and Lynch (47) reviews published preclinical studies regarding various drugs of abuse, including methamphetamine and ATS. The researchers state that aerobic exercise correlates negatively with drug abuse and is associated with decreased substance self-administration in all phases of addiction (from acquisition to relapse) in rats. The authors conclude by claiming that it is still not entirely clear when should exercise be introduced in the overall process for the best possible efficacy and what quantity is needed, although ultimately it seems that any amount would have a positive effect, on both sexes, with earlier introduction relating to long-term protective effects and significant benefits even in sedentary subjects. Another recently published paper concluded that five weeks of exercise (swimming protocol) on an animal model (rat), after exposure to amphetamine, led to lower relapse rates and attenuated anxiety-like symptoms associated with drug abstinence (21). Additionally, it was suggested that exercise promotes modulation of membrane plasticity and adjustment of Na^+/K^+ pump activation.

Miller et al expand earlier findings on stimulant abuse and exercise. The authors intended to found if access to an activity wheel could diminish intravenous d-methamphetamine self-administration in male rats having previous wheel exercise experience. It was found that access

to an activity wheel simultaneously with the start of intravenous drug administration resulted in reduced self-administration of METH (48). There are a few preclinical studies on the sex differences regarding exercise and drug intake with relevant results. For example, female rats have shown less cocaine self-administration than rats, in programs comprising voluntary wheel exercise (49). This could potentially be of concern regarding sex-related preferences and characteristics on the practice of exercise.

Another paper focused on the role of exercise on cardiotoxicity induced by d-amphetamine on rats (50). The researchers pointed out extensive cardiotoxicity induced by this stimulant, but the exercise group presented less severity in those lesions, with lower markers of oxidative stress apparently because of increased reduced glutathione on active subjects, thus providing yet another factor adding to its protective role. O'Dell and Marshall give some more insight in two very recent papers (20,51). Firstly the authors, along with other researchers, found significant improvement in striatal dopamine and cortical serotonin neuron terminals in exercised rats after methamphetamine-induced lesions. The authors elaborated a protocol consisting in a binge regimen of the drug and a program of 3 weeks of free access to a running-wheel before and 3 weeks after METH injections (20). Trying to unravel a physiological explanation behind these findings, three mechanisms were hypothesized by the same researchers (20,51). Firstly, changes induced by exercise before a binge regimen could decrease in some way the acute effects of METH, by intervening in the pharmacodynamics and biodistribution of the drug. Secondly, physical activity before the methamphetamine injection could stimulate the synthesis of protective factors against damaged monoamine nerve terminals, for example by intervening with enzyme activity and the oxidative stress system. However the researchers found that physical exercise prior but not after a binge regimen failed to protect against METH-induced dopaminergic damage in laboratory rats (51). Finally, exercise could

promote expression of growth factors that would restore METH-induced lesions. This last hypothesis seems the most plausible, and is developed later in this review.

Also worth mentioning is the fact that exercise needs to happen within certain boundaries to be beneficial, as Lynch *et al* propose in a comprehensive review: it was demonstrated that intense and long-lasting exercise can be harmful instead of helpful, as seen with methamphetamine self-administration increasing in rats when exposed to such high-intensity conditions (52).

The general benefit of exercise in drug abuse only takes effect if the population of drug users are willing to take part in such program. In fact, the majority of drug users show interest on the practice of exercise (75 per cent according to one study) with some limits that need to be taken into account: cost of subscription to a gymnasium and equipment, motivation, available time and transport. In another study (53) the majority of individuals claimed walking as a preferred method of exercise, with lack of motivation being one of the biggest restrictions to exercising.

Many ways can be used to increase motivation, such as using a pedometer or cash or other type of incentives. However, the limits described by these studies can be actively brought down, as exercise can be inexpensive and flexible according to the subpopulation in treatment; also it has the advantage of not having the side effects experienced with pharmacotherapy (54). Sex differences also dictate whether a specific exercise program is more accepted than other. Men usually prefer exercising alone (contrasting with women) and are not as willing to be supervised as women. Males also prefer strength training and running while females prefer aerobics and yoga. The preventive role of exercise is also of high importance to the addiction process (55). For instance, in the teen subpopulation exercise decreases the likelihood of experimenting illicit drugs and tobacco use (52). Cognitive impairment seen in substance use disorder probably shows improvement with physical exercise, as in a subpopulation of healthy subjects cognitive performance is better in the fittest. Chang and colleagues studied the effect of aerobic exercise

on cognitive performance in a population of 36 healthy young college students separated into three groups of variable fitness; following previous conclusions, the authors stated that cognitive performance improved on all groups, with better outcome in the group who practiced acute moderate intensity exercise (56).

Relevant clinical studies have been increasing in the last decade. Dolezal and colleagues appear to have been the first to study fitness markers on methamphetamine users, such as heart rate variability (HRV) among methamphetamine-dependent users under behavioural therapy (57). HRV is a marker of autonomic nervous system function on heart rate, consisting in changes in the interval between heart beats over a period of time. The researchers found that 8 weeks of exercise improved HRV in these individuals, translating a restitution of the physiologic sympathetic and parasympathetic function. Improvement in VO_{2max} has also been noticed in these users: the authors point an increase of 24 per cent in this parameter, associated with increases in endurance and muscle strength. This supports even further the role of exercise as a preventive as well as a treatment option including the management of cardiovascular disorders induced by methamphetamine exposure. A pertinent premise brought up by the authors is the fact that physical exercise has proven benefit in psychiatric diseases, and can therefore help METH users that suffer from such conditions. Another study by Dolezal and colleagues (58) with a group of 39 METH-dependent users under residential treatment provided some promising findings. Besides improved fitness measures (VO_2 max, endurance and strength) on exercised individuals, treatment outcome was markedly improved on these users, with decisive recommendations: supervised and well-structured exercise programs are a must to achieve positive outcomes. The control group, without structured activity, failed to attain significant changes in performance and body mass. Two unpublished studies (as of March 2015) by Richard A. Rawson and colleagues further develop the influence of exercise on methamphetamine dependence. In one of them, the researchers wanted to evaluate the role of a

structured exercise program on anxiety and depression on abstinent METH-dependent users (59). Findings were positively similar to those described before; individuals who took part in more exercise sessions showed better improvement of symptoms than the ones who took part in a less number of sessions. As shown in previous studies, there was a significant improvement on fitness measures among those participating in these exercise sessions. Despite this optimistic outcome, the authors state some limitations to the study: only users under residential treatment constituted the sample; therefore the same conclusions may not be seen in outpatient care or users who do not seek help at all. Also, the diagnostic of psychiatric disorder (anxiety and depression) did not take into account the DSM-IV reference textbook. A second study by Rawson *et al* (60) also concerned an 8-week exercise program for METH-dependent users under residential treatment focusing on the efficacy of this program as a potential therapy. The population of users was subsequently divided in several severity groups according to days of drug use in the past month. The low severity group (< 18 days) showed lower relapse rates either at one or three months after discharge of the exercise program. Users who participated in more sessions also maintained longer abstinence at follow-up. Sustained abstinence was seen in users who reportedly continued exercise at one-month follow-up, more so than users who did not report pursuing any exercise activity after discharge.

Despite the need for more studies (61), with an ever-growing body of evidence for the past few years it is rather safe to assume that exercise as a conjoint therapy would probably bring higher efficacy to the overall treatment of substance use disorder (43). Additionally it seems plausible that well-designed exercise programs aimed at specific subpopulations of users would translate into higher adherence and better results. Overall, table 1 highlights the beneficial outcomes from physical exercise in drug users including METH users.

Table 1. Evidence of physical exercise on substance use disorder

Reference	Sample	Type of Exercise	Duration	Drug of Abuse	Outcome
Weinstock et al. (2008) (62)	45 exercisers 142 non-exercisers (n=187, all under contingency management treatment)	User self-selected activities thus classifying them as exercisers (e.g. planning workout routine, basketball, swimming, jogging) or non-exercisers (paying rent, attending doctor's appointment)	12 weeks	Alcohol, cocaine and opioids	25% completed at least one activity; exercisers had longer abstinence periods
Brown et al. (2010) (54)	Cohort of 16 previously sedentary drug-dependent users, not taking any medication that could interfere with the results (n=16)	Supervised aerobic exercise program in a treadmill started at 20 minutes and increasing to 40 during the 12-week period; moderate intensity defined by 55-69% age-predicted maximal heart rate. There were also group sessions (15-20 minutes of duration) and exercise outside the facility was promoted	12 weeks	Alcohol, cocaine, marijuana, opioids, sedatives	Almost 60% completed all 12 weeks. 66,7% had not relapse at the end of the program; ↑ metabolic equivalents; ↓ body fat and body mass index
Dolezal et al. (2013) (58)	29 users finished the proposed program, resulting in a 74% adherence rate; 15 elements in the exercise group and 14 in a health education group with no exercise (n=39 individuals)	Endurance training: first 3 weeks jogging and/or walking on treadmill during 30 minutes, at intensity based on heart rate; the subsequent 5 weeks had increasing intensity Resistance training: after the endurance training session; progressive circuit-type program with selectorized machines and/or dumbbell training	3 days /week, 8 weeks	Methamphetamine	Improvement of VO_{2max} (↑21%) as well as muscle strength and endurance. Reduced percent relative body fat (↓15%); reduced fat weight (↓18%)
Flemmen et al. (2014) (41)	12 substance-dependent users in the training group; 12 in the control group with conventional rehabilitation treatment (n=24, all in a clinic at the time of inclusion)	Treadmill interval training in 4x4 minutes at 90-95% of maximal heart rate (high intensity)	3 days/week, 8 weeks	Not specified	3 users in the training group and 5 users in the control group dropped out. Aerobic power at baseline was lower than on the average population. Improvement of VO_{2max} (↑15%) and in depression was apparent on the training group
Dolezal et al. (2014) (57)	28 users under residential treatment divided into two subgroups of 14 elements, one subjected to exercise intervention and the other	Supervised endurance and resistance training (1-repetition maximum and 85% of 1-repetition maximum for chest and legs)	8 weeks	Methamphetamine	HRV was reduced in recently abstinent users; after the 8-week period HRV markedly increased, VO_{2max} increased by 24%, muscle strength and

	took part in health education sessions; these were compared to 22 age-matched, drug-free, sedentary controls (n=50, all males)				endurance for upper and lower body also raised
Rawson et al. (Not yet published) (59)	135 dependent-users under residential treatment were randomly assigned to an exercise (69 users) and a health education group (consisting in 24 1-hour sessions given by a trained health-educator) (66 users)	Endurance (30 minutes on a treadmill) followed by resistance (15 minutes of weight training)	3 days/week, 8 weeks	Methamphetamine	Significantly reduced depression and anxiety symptom scores (according to Beck scales)
Rawson et al. (Not yet published) (60)	135 dependent-users under residential treatment were randomly assigned to an exercise (69 users) and a health education group (consisting in 24 1-hour sessions given by a trained health-educator) (66 users)	Endurance (30 minutes on a treadmill) followed by resistance (15 minutes of weight training)	3 days/week, 8 weeks	Methamphetamine	Median of attendance = 16 sessions. Better treatment compliance and continued exercise after the proposed program resulted in longer abstinence and lower relapse rates; fewer exercise group users had positive samples for METH use at 1-month and 3-months follow-up, although these findings were not statistically significant

8. Neurobiology of Exercise on Drug Abuse

As stated earlier, benefits of physical exercise extend to the CNS. In fact, exercise has neuroprotective and neurogenerative effects, via expression of genes and subsequently growth factors and neurotrophins that prevent neuron injury (in several brain structures such as the hippocampus and striatum) and trigger the development of new cells (40). Neurotrophins include the brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) which are increased by physical activity (40,51). BDNF regulates synaptic plasticity and has some influence on the process of addiction. During abstinence its levels rise in mesolimbic structures of the brain following a nadir, stimulating drug-seeking behaviour. With exercise, expression of the BDNF gene increases and epigenetic mechanisms take action (via acetylation of histone 3 and decreased methylation in the promoter IV region of the BDNF gene), thus offsetting the initial decrease in BDNF during early withdrawal seen in the reward pathways (47,52). It is suggested that exercise could prevent BDNF expression seen in abstinence, thus suppressing drug-seeking behaviour (52). Its effects have been studied in alcohol, cocaine and METH users, suggesting it could be a potential abstinence biomarker (63). GDNF also increases in exercised animal models, and seems to provide a positive effect on striatum recovery after methamphetamine-induced neurotoxicity, as seen by raised dopamine levels after injection of this neurotrophic factor in the striatum of rats (51).

As mentioned before, dopamine increase in the nucleus accumbens seems to be one of the main mechanisms leading to addiction. Thus, exercise can act as a healthy positive reinforcer. A review by Lynch *et al* thoroughly describes the ways exercise interferes with the reward pathways (52). Chronic exercise elevates tyrosine hydroxylase levels (64), increasing dopamine in many CNS regions; preclinical studies show activation of dopamine neurons in the VTA and

higher levels of dopamine in the nucleus accumbens in animals submitted to wheel running; it also increases levels of ΔFosB (which plays a predominant role in the development of addiction) and upregulates D_1 receptors and D_2 receptors (65). The increase in both dopamine receptors (D_1 and D_2) might be beneficial to chronic METH users by restoring unbalanced density of these receptors. Also, expression of DAT is decreased in the midbrain of exercised subjects, which leads to higher dopamine availability in the synapse, further supporting physical exercise as an alternative positive reinforcer (64).

Other catecholamines also take part in the overall process of addiction. Norepinephrine is crucial in the relapse phase after abstinence; exercise manages to decrease norepinephrine levels in the frontal cortex. Glutamate is a modulating agent in drug-seeking behaviour and relapse and decreases with chronic drug use. Exercise brings its concentration back to normal, as seen with ischemia models, similar to the conditions seen in chronic drug abuse (52). The opioid system comprising three types of receptors (delta, kappa and mu) and opioid peptides (endorphins, enkephalins, dynorphins) are ubiquitous in the CNS. Endogenous opioids increase with physical exercise improving mood states, and there is evidence of diminishing exogenous opioids use after physical activity (47). For instance, opioid neurons and receptors are present in the arcuate nucleus and project to several regions, from the limbic system and basal ganglia to the brainstem, specifically VTA (66). This system revolves around the sense of pleasure (hedonics) among others, which constitutes a vital part of addiction and reward, and is intimately intertwined with dopamine release in the CNS, as opioid receptors (delta) are overexpressed by exercise thus inducing dopamine release in the nucleus accumbens (64,67). As described earlier, METH abuse leads to serious cardiovascular impairment. In addition, it is capable of disrupting the blood-brain barrier, mainly at a cortical and hippocampal level, via increased production of reactive oxidative species, leading to altered permeability of the barrier. One recent study by Toborek *et al* (68) verified that physical exercise did offer protection

against this severe damage to the blood-brain barrier in mice injected with METH. Non-exercised subjects presented lower levels of glutathione in the brain capillaries whilst exercised subjects had marginally higher base levels but showed signs of marked improvement after METH injection, by raising antioxidant capacity of these capillaries under such circumstances. The authors also confirmed previous findings of reduced tight junction protein (e.g. occludin, claudin-5 and ZO-1) expression after methamphetamine administration, which explains the disrupted barrier and posterior inflammatory response in the brain on these subjects. On the same study it was shown that exercise did lessen those changes. Also, it was demonstrated that a transcription factor that triggers antioxidant mechanisms (Nrf-2) is overexpressed by physical exercise

Neurogenesis and gliogenesis in the hippocampus is promoted by aerobic exercise. This is relevant because reductions of hippocampal neurogenesis are associated with increased drug self-administration. It also increases gliogenesis in the prefrontal cortex of rats, which has major influence on relapse and drug abuse (47). A study correlating both exercise and METH aggression to the prefrontal cortex concluded that the quantity of practised exercise is not as important as actually being physically active vs not being active on medial prefrontal cortex plasticity; the same study ends by suggesting that voluntary exercise may therefore reverse reduction of gliogenesis in chronic METH users (22).

Conclusion

To this date there is no pharmacological treatment directed specifically to methamphetamine dependence, thus relying on general drugs used in other dependence treatments and on behavioural 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, cannabis and cocaine use. Regarding methamphetamine, only in the past few years pertinent preclinical and clinical studies have been conducted addressing this drug specifically. Overall, there were great improvements demonstrated in active users, with better fitness measures, lower relapse rates and sustained abstinence when compared to non-exercised individuals. Further studies are profoundly needed, to confirm reproducibility of previous findings: stablish the most efficient exercise program, attending to sex, age and mental consequences of chronic use (there are significant differences among men and women drug users), namely duration, intensity (it appears moderate intensity exercise is the best to begin with), type (no studies focus on anaerobic exercise vs aerobic, with positive findings related predominantly to aerobic programs) and need of supervision (structured programs apparently have better outcomes) and association with current treatments (most clinical studies happen under residential treatment).

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