



**UNODC**

United Nations Office on Drugs and Crime

# TREATMENT OF STIMULANT USE DISORDERS: CURRENT PRACTICES AND PROMISING PERSPECTIVES

*DISCUSSION PAPER*







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## EXECUTIVE SUMMARY

There is a growing concern in many parts of the world for the large-scale use of psychostimulants for non-medical purposes and high incidence of psychostimulant use disorders (PSUD), also known as stimulant abuse, dependence or addiction. The number of individuals that regularly use psychoactive substances such as cocaine, amphetamines, methamphetamines and other psychostimulants is greater than the number of individuals using opioids and opiates. In spite of this high prevalence, individuals with psychostimulant use disorders around the world are provided minimal or non-existent contact with health and social institutions and very poor treatment programs. In many countries, treatment services for substance use disorders have been designed for treatment of opioid and alcohol dependence and are not tailored for stimulants dependence. In particular, the model including medical interventions and social protection has seldom been applied for these individuals, making the services not appealing and attractive for the clients.

While medical models of treatment for individuals with alcohol or opioid use disorders are well accepted and implemented worldwide, in most countries there is no parallel, long-term medical model of treatment for individuals with stimulant use disorders. Medical interventions are often used to treat medical and psychiatric complications of stimulants use, however a comprehensive, medically oriented approach that includes psychosocial and pharmacological interventions to specifically treat PSUD has not yet been developed.

An existing and well-developed model of treating individuals with opioid use disorder, using pharmacological and psychosocial interventions, has been endorsed as best practice by the WHO and most professional organizations and it has been disseminated to many regions. The existing model of treating opioid use disorder can provide wealth of experience in adapting programs to individual communities working with patient population. This would permit to develop a range of treatment services, and workforce qualification that can be utilized in the parallel model to treat individuals with PSUD.

Currently used approaches to treat stimulant use disorders are still poorly organized and not based on behavioral interventions but on long-term residential treatment, at times involuntary. Most of existing services are relying only on psychosocial strategies, often not effective and not integrated with pharmacological interventions and social support.

The result of this condition is that most patients are not encouraged to attend treatment programs and never come in contact with treatment facilities. The impact of problematic stimulant use disorders remains on individuals, their families, and the society. In some cases, Member States are allocating the necessary resources for treatment centres targeting these population, but the outcome is very minimal and involving a tiny minority of the people in need.

In response to requests from Member States, a group of experts from 25 countries and UNODC staff met to share their views and develop this discussion paper on the treatment of PSUD that

outlines the existent comprehensive interventions, including the use of promising medications. The group collected existing scientific evidence and practitioners' opinions formulating preliminary suggestions for integrating psychosocial and pharmacological therapy.

The group of experts suggested to accompany the integrated treatment programs with comprehensive social services (social protection, housing, food, incentives etc.), together with a broad range of strategies aimed at reducing the negative health and social consequences of stimulants use.

In addition, the group indicated the importance to involve individuals who are affected by PSUD in designing and planning the most acceptable and appealing treatment interventions.

The discussion paper aims at raising awareness about the latest scientific evidence concerning the treatment of this large and vulnerable population and makes a call for action to Member States to consider expanding specific treatment options and medical interventions.

Finally, the experts suggested the establishment of an international network of treatment sites to conduct implementation research on the proposed medical model of treatment across developed and developing countries.

## DOCUMENT BACKGROUND

### Document Purpose

The aim of this discussion paper is encouraging Member States to explore the response to the extensive use of psychostimulants at the global level and the high prevalence of psychostimulants use disorders.

There is no universally accepted evidence-based treatment model that integrates the psychosocial and medical approaches and offers treatment to individuals depending on psychostimulants that parallels treatment of alcohol and opioid use disorders. This condition is particularly dire in developing countries where there is a rapidly increasing population of individuals regularly using stimulants and developing stimulant-related psychiatric and medical problems. The result of this condition is that most patients are not encouraged to attend treatment programs and never come in contact with treatment facilities. In some cases, Member States are allocating the necessary resources for treatment centres targeting these populations, but the outcome is very minimal and involving a tiny minority of the people in need, due to the uncertain and fragmented medical response. In other cases, the only available response is based on forced residential treatment and long-term abstinence.

To address this issue, the UNODC Prevention, Treatment and Rehabilitation Section organized a meeting of experts to discuss existing and promising approaches to treat PSUD. The meeting was supported by the UNODC Project GLOJ71: TreatNet II. It took place at the Vienna International Centre from 17 – 19 October 2017 and brought together 40 participants, mainly leading experts on the treatment of PSUD from 25 countries. During the three-day meeting the experts made formal presentations and exchanged experiences summarizing traditional and novel treatment approaches to psychostimulants that have been implemented across different countries and discussed integrated models of treatment that may be effective and suitable for implementation in a variety of settings once translated and culturally adapted.

### Expert suggestions

The experts suggested the necessity to develop a specific, comprehensive, technical assistance guidance tool on psychostimulants dependence treatment which is globally applicable and based on scientific evidence and appropriate clinical practice. This discussion paper could form the basis for developing technical support initiatives and materials. The preparation of a concise document is necessary to summarize the existing evidence and propose a flexible approach to plan treatment programs and related observational studies.

Experts highlighted that offering integrated psychosocial and pharmacological treatments based on the medical model and supported by the scientific evidence will attract affected



individuals to treatment and significantly alleviate the impact of stimulant use on individuals, their families, and the society.

The evidence shows that drug use disorders in general, are best managed within a public health system, similarly to other medical problems, in particular other chronic disorders. However, barriers to implementing such a model include: poor integration of substance use treatments with the health care system, limited number and capacity of trained health care professionals, and lack research on implementing evidence-based treatment for psychostimulant use disorder in the “real world,” healthcare settings. Moreover, outdated views of substance use disorders persist in many parts of the world which lead to widespread stigma and discrimination of individuals seeking treatment.

## PSYCHOSTIMULANTS OVERVIEW

Stimulants is a class of substances acting on the central nervous system to increase alertness, attention and energy with both positive mood properties and arousal attitude. Their mechanism of action is in general to increase the activation of natural stimulating pathways in the brain, in particular enhancing the function of noradrenaline, adrenaline and dopamine. These mono-amines are responsible for the sympathetic reaction to stress, the metabolic correlates of aggressiveness and fear and the rewarding mechanisms of the motivational system.

In specific, pharmacological stimulants are able to increase the synaptic level of stress mono-amines facilitating their release, reducing their re-uptake by the brain cells and enhancing their ability to stimulate receptors. The continuous and intensive stimulation of the stress response due to these pharmacological agents may induce the depletion of natural stimulants and the impairment of the sympathetic response.

Stimulants can be extracted from plants, synthesized in the laboratory or being the result of semi-synthetic processes. On one side, some of the plant-based stimulants, such as cocaine, ephedra, or khat, continue to be widely used in our society. On the other side semi-synthetic psychostimulants have been prepared starting from the active principles contained in the natural products, such as ephedrine and cathinones. Finally, chemists were able to synthesize substances, such as amphetamine and methamphetamine in the laboratory. Psychostimulants are used to treat a limited number of medical disorders but are also used for non-medical purposes.

### Types of Psychostimulant Substances

#### COCAINE

Cocaine is an alkaloid that naturally occurs in the leaves of the coca bush that grows in the mountain regions of South America. Coca leaves can be chewed after light roasting and adding lime or plant ash to increase absorption of cocaine. Leaves can be also processed using various chemicals to produce cocaine (coca) paste which contains high concentration of pure cocaine alkaloid. Coca paste can be smoked, but it is primarily used to manufacture other forms of cocaine.

Cocaine can be converted to a salt form by mixing it with an acid. Cocaine salt, in a form of a powder, can be used either by snorting, rubbing on the gums or dissolved in water and injected. Adding organic solvent and heating it with a base converts cocaine salt into cocaine base which is usually in form of small crystals. This form of cocaine does not dissolve in water, so it cannot be injected but it can be heated up, as it easily



melts and converts into vapor (smoke crack cocaine), which then allows it to be inhaled into the lungs.

The continuous exposure of vulnerable individuals to cocaine is able to induce a strong addictive behavior with a compulsive conditioned mechanism. Furthermore, cocaine may induce irritability, insomnia, paranoid thinking, lack of behavioral control and sense of omnipotence, prone to violence and suicide thinking. In case of prolonged heavy use, the depletion of sympathetic mono-amines is reflected by abulia, fatigue and inability to daily activities. Cardiovascular disorders may characterize the clinical picture of cocaine use disorders, particularly with the risk of arrhythmias, myocardial infarction and stroke.

Cocaine is under control in the International Law in a very limited medical use (local anaesthesia).

## **KHAT**

Khat is derived from the large bush of a Catha family growing in East Africa. It contains cathinone, a cathine, and norephedrine, natural stimulant alkaloids. Fresh leaves can be chewed without preparation, brewed for drinking, crushed and made into various mixtures for eating, or smoked either alone or mixed with hashish or tobacco. Cathinone has been described as the “natural amphetamine” with the primary effect of increased energy, mild euphoria, and wakefulness and its use has a long tradition among some ethnic groups. Typical patterns of khat consumption range from moderate to problematic use; excessive forms are associated with a use disorder and psychotic symptom presentations. In its pure form, cathinone is classified as a Schedule I-controlled substance with no medical use. The semi-synthetic products obtained from cathinones have generated a large group of dangerous drugs, such as methyl-cathinone (mephedrone) with possible serious cardiovascular and mental health problems. Mephedrone overdoses have been commonly reported in Europe and around the world.

## **EPHEDRA**

Plant from the Ephedra family grows primarily in Europe, Asia and Americas and contains ephedrine and other natural substances with mild stimulant properties. Extracts from the young branches of the plant containing ephedrine can be manufactured into capsules or liquid extracts. Ephedrine has a pharmacological effect similar to cocaine or synthetic amphetamines and is often sold as a safer alternative to other stimulants. Products containing ephedrine are promoted as weight-loss agents however the use of these products can have severe cardiac and neurologic adverse consequences. Ephedrine has been banned in many countries and it is classified as a controlled substance in some US states.

## AMPHETAMINES AND METHAMPHETAMINES

Because of the many desired properties of plant-based stimulants, a substantial effort was devoted to the replication and expansion of the various psychostimulants using methods of synthetic chemistry. After ephedra was extracted and characterized, chemists were trying to improve upon it and in 1910's have synthesized amphetamine in Germany and methamphetamine in Japan. Both of those substances were found to have a potent stimulant and euphoric properties and were first patented as medicines (Table 1). Later, chemists continued to modify the amphetamine molecule in an effort to maximize some of its pharmacological and psychoactive properties developing a wide range of medications as well as psychoactive substances with potent psychoactive properties but limited medical benefits.

Amphetamines were initially used to treat asthma and sinus congestion, to decrease appetite, and to treat depression, parkinsonism, or narcolepsy. However, amphetamines were frequently used to improve mood and enhance performance (e.g., to combat sleepiness and to aid soldiers in battle by eliminating the need for sleep) rather than to treat disorders. Initially, amphetamines were considered to be medical miracles which led to a widespread use. With a widespread use it became evident that a significant number of individuals who used large doses of amphetamines and/or use them repeatedly, develop serious negative psychiatric and medical complications, including addiction, psychosis, and seizures. To limit these adverse effects, amphetamines and related medications were rescheduled as controlled substances under International Narcotic Laws and the medical use of prescription stimulants began to wane.

As the medical use of amphetamines became limited, these substances were synthesized illegally and were distributed for recreational use. Various amphetamines, mainly methamphetamine, can be synthesized in a non-industrial, non-pharmaceutical, relatively simple and rudimentary laboratories using easily available materials, reagents, and chemical preparation processes.

Illicit amphetamines are mostly taken orally as tablets or capsules and tablets can be crushed and snorted or injected. Methamphetamine is also available as highly pure crystalized form, known as crystal methamphetamine, which can be inhaled or smoked. Methamphetamine powder can also be dissolved in water and injected intravenously.

One of the better-known amphetamine-derivatives with hallucinogenic properties is *MDMA* (ecstasy). It has been used medically in 1970's but due to its widespread unsupervised or recreational use *MDMA* has been rescheduled in 1980's and classified as a substance with no medical use. Ecstasy continues to be sold as a drug utilized for non-medical purposes, often during the dance parties. However, the drug sold as ecstasy frequently contains other synthetic analogues of amphetamines with psychoactive properties, and there are wide regional variations in the content and purity of illegally sold products.

## **OTHER STIMULANT-LIKE MEDICATIONS**

Other amphetamine derivatives with limited stimulant properties were also synthesized and developed as medications. For example, an antidepressant and smoking cessation medication bupropion, has mild stimulant properties but is not a controlled substance. Another medication that is often grouped with psychostimulants is modafinil which has a different chemical structure than amphetamine but has similar clinical effects (promoting alertness) and pharmacological properties (increasing synaptic mono-amine concentration). Modafinil is also classified as a controlled substance.

### ***New Psychoactive Substances (NPS)***

Psychoactive, synthetically produced substances, also known as "designer drugs", "legal highs" or "research chemicals", are subsumed under the name "New Psychoactive Substances" (NPS). The term "new" refers to substances that have recently become available rather than substances newly synthesized. These substances have similar effects to drugs under international control and are often molecular modifications of already known illegal drugs (e.g. cannabis, cocaine, LSD) or substances with completely new chemical structures. Legal controls and the ability to detect NPS are limited which poses a major challenge.

NPSs group includes substances with stimulant properties in addition to substances with cannabinoid, opioid, or hallucinogenic effects. Stimulant NPS include synthetic cathinones such as mephedrone or MDPV, amphetamine analogues, and analogues of tryptamine including 2C-B, and the benzofurans, which may have both stimulant and hallucinogenic properties (Dawson et al., 2014; Sahai et al., 2016)

## **Medical Use of Pharmaceutical Stimulants**

Various pharmaceutical preparations of amphetamines, methamphetamine, and a related medication methylphenidate are available in some countries for a legitimate medical use. These medications are approved to treat attention deficit hyperactivity disorder (ADHD), sleep-disorders such as narcolepsy and excessive sleepiness, obesity, and binge-eating disorder. However, all prescription stimulant medications have a potential for misuse and can produce adverse effects. These medicines can be diverted from legitimate sources and used to enhance the performance of individuals who do not have a disorder indicated for these medications. Diverted amphetamines can also be used to produce euphoric effects, in which case tablets are crushed and either snorted or injected.

## EPIDEMIOLOGY

### Overview and Global Psychostimulant Burden

About 275 million people worldwide, which is roughly 5.6% of the global population aged 15–64 years, used drugs at least once during 2016. Some 31 million people who use drugs suffer from drug use disorders, meaning that their drug using behavior is harmful to the point where they may need treatment. Moreover, an estimated 34.2 million people had used amphetamines (including methamphetamine, amphetamine and misuse of prescription stimulants), 20.6 million people had used ecstasy and 18.2 million people had use cocaine. In total, an estimated 73 million are past year users of stimulants, in comparison with around 34 million of opioid and opiate users, though polydrug use is a common feature among individuals using drugs.

The Global Burden of Disease data for 2018 estimates that 27 million DALYs (disability adjusted life years) are attributed to drug use disorders of which the majority are attributed to opioids use disorders. Approximately 1.2 million DALYs are attributed to amphetamine use disorder and less than a million DALYs to cocaine use disorder. However, the overall burden of disease attributed to psychostimulants use disorders appears to be grossly underestimated due to the way the burden of disease is estimated (burden attributed to use of opioids and frequent polydrug use). However, the overall burden on disease (DALYs) attributed to amphetamines use disorders increased by one third over 2010 -2018. Furthermore, the overall system for recording mortality data attributed to substance use remains poorly developed in many regions and becomes more challenging with regard to reporting causes of deaths attributed to cocaine or amphetamines use. Despite these gaps drug related deaths attributed to amphetamines are ranked as 2<sup>nd</sup> after opioids in most countries in South East Asia and 3<sup>rd</sup> among most countries in Europe. Also, data on trends in drug related mortality from the United States, as an example, indicates that between 2007 and 2018 there was an 8 percent increase in deaths attributed to methamphetamine especially in cases involving opioids.

Studies have found that people who use cocaine or amphetamine engage in higher-risk sexual behaviors and have similar HIV prevalence than people who inject opioids. Those individuals have more sexual partners and more frequent intercourse with casual partners and regular partners than PWID who inject other drugs. Moreover, a systematic review found that the risk of acquiring HIV was more than 3 times greater among people who injected cocaine than among non-injecting cocaine users, and 3.0 times greater among people who injected amphetamines than among non-injecting amphetamines users. Psychostimulants especially methamphetamine and mephedrone also figure quite prominently among groups of men who have sex with men (MSM) engaging in “Chemsex” – a term used to describe use of specific drugs before or during planned sex to facilitate, disinhibit, prolong or sustain or intensify sexual experiences. There is strong evidence of higher risk sexual behaviours and higher HIV prevalence among MSM who use amphetamines than

among MSM who use other drugs. Thus, the burden of disease attributed to psychostimulants could be much higher than actually estimated.

The use of psychostimulants also figures prominently within the polydrug use phenomenon especially their use with depressants such as opioids or alcohol to alter the positive effects or reduce adverse effects of psychostimulants. Also, the concurrent or sequential injecting of psychostimulants such as amphetamines and opioids is of concern because of increased risk of HIV, overdose, and other negative health consequences.

For the reasons mentioned above and the lack of pharmacological treatment of psychostimulants the institutional response to substance use disorders in most regions has focused primarily on opioids in general. The large population of individuals who only use stimulants have not received the necessary attention or access to appropriate and specific treatment programs.

## Psychostimulant Use

### COCAINE

Globally, an estimated 18.2 million people or 0.4% of the population aged 15–64 years used cocaine over the previous year. The use of cocaine remains concentrated mainly in North America and South America, where, respectively, an estimated 1.9% and 0.95% of the population aged 15–64 years were estimated as past-year users, followed by Australia and New Zealand (2.2%) and Western and Central Europe (1.2%). In recent years, there are indications of an increase in cocaine use in many countries in North and South America as well as in Western and Central Europe. In addition, the use of cocaine base paste, previously confined to cocaine-manufacturing countries, has spread to many countries in South America. Though prevalence data from most countries in Africa and Asia are not available, in parts of Asia and West Africa, increasing amounts of cocaine have been reportedly seized, which indicates that cocaine use could be taken up, especially among the urban affluent segments of the population in regions where its use had been low or uncommon.

### **AMPHETAMINE-TYPE STIMULANTS: AMPHETAMINE, METHAMPHETAMINE, ECSTASY, AND RELATED-SUBSTANCES**

Illicit amphetamine-type stimulants include a great variety of substances with the main groups including amphetamines (amphetamine and methamphetamine), ecstasy and synthetic new psychoactive substances (NPS) that are stimulants. In 2016, an estimated 34.2 million people (0.7% of the adult population) had used amphetamines (amphetamine, methamphetamine and misuse of prescription stimulants), and 20 million people had used ecstasy. There is a wide variability in the type and prevalence of stimulant-type substance use across regions (Table 1).

**Table 1.** Type of psychostimulants used in different regions

Regions	Type of stimulants used
<b>Africa</b>	<b>Cocaine, methamphetamine</b> , and cocktails containing crack cocaine and cannabis, limited use of ecstasy, khat in some parts
<b>North America</b>	Cocaine, methamphetamine prescription stimulants, ecstasy and amphetamine
<b>Latin America and the Caribbean</b>	<b>Cocaine</b> , cocaine base paste, <b>prescription stimulants</b> , amphetamine, methamphetamine, ecstasy
<b>East and South East Asia</b>	<b>Methamphetamine</b> (crystal and pill) ecstasy and stimulant NPS, limited use of cocaine
<b>Central Asia and Transcaucasia</b>	Limited amphetamine, methamphetamine and ecstasy
<b>South West Asia</b>	<b>Methamphetamine</b> (also with opioids), limited use of ecstasy or cocaine
<b>Near and Middle East</b>	" <b>Captagon</b> " (amphetamine), limited use of methamphetamine, prescription stimulants, cocaine, and ecstasy
<b>Western and Central Europe</b>	<b>Cocaine</b> , mainly <b>amphetamine</b> and methamphetamine in some countries e.g., Czechia, <b>ecstasy</b> and stimulant NPS
<b>Eastern Europe/South Eastern Europe</b>	<b>Cocaine</b> , amphetamine, methamphetamine, ecstasy
<b>Australia and New Zealand</b>	<b>Methamphetamine</b> (crystal and powder), prescription stimulants, <b>ecstasy</b> , <b>cocaine</b> , and stimulant NPS

The use of amphetamines is reported high in Australia and New Zealand (1.3%) and North America (2%). In Asia though the annual prevalence (0.6%) is comparable with the global average, due to the population size an estimated 17.5 million amphetamines users – half of the global estimated number - reside in Asia. In recent years there are indications of an increase in methamphetamine use in North America, and the increase in the use of methamphetamine, in particular of crystal methamphetamine, in East and South-East Asia. The use of amphetamines in Western and Central Europe has remained overall stable.

The use of ecstasy is also limited to a few regions and is reported high in Australia and New Zealand (2.2%), North America (0.9%) and Western and Central Europe (0.8%). The use of "ecstasy" is mainly associated with recreational nightlife settings, with higher levels of use seen among young people in urban settings. In recent years, with an increasing availability of high-purity ecstasy in the Western and Central Europe as well as in other sub-regions, there are indications of an overall resurgence in ecstasy use. The forms of ecstasy have also diversified with high purity powder and crystalline forms of the drug commonly available and used. For most countries the prevalence of stimulant NPS is not available. Nevertheless, it is important to consider that stimulant NPS are an ever-growing category of substances among the NPS reported by countries and currently account for more than one third of NPS identified and reported to UNODC. The shift in countries especially in South East Asia from primarily using opioids and other depressants of the central nervous system to using psychostimulants or along with opioids has presented a challenge and added another dimension to the world drug problem



In spite of the high prevalence of stimulants at the global level, the rate of those who are seeking treatment among people affected by PSUD is extremely limited with respect to those with opioid use disorders. Stimulant use and its consequences have therefore brought attention to many governments and organizations and have resulted increased research efforts especially with regard to effective pharmacological and psychosocial treatment of psychostimulants use disorders.

**Amphetamine tablets** were originally used as medicines with one of brands known as Captagon and consequently, “captagon” started to be used for a variety of amphetamines sold in tablet forms, mainly consumed in the Near and Middle East. Most tablets seized as “captagon” contained amphetamine, in combination with caffeine and occasionally with other adulterants. In many countries in South-East Asia a frequently used amphetamine type stimulant comes in a form of amphetamine tablets which are called by various names, often translated to English as “horse pill.” Amphetamine is also the common substance used in Western and Central Europe and the non-medical use of prescription stimulants is also reported from North and South America.



**Ecstasy (MDMA) Tablet** is the form used by the vast majority of “ecstasy” users. It can be found in Americas, Europe, East and South-East Asia and Oceania. Powder form or crystalline MDMA (“crystal/rock”) has the form of capsules containing powder or crystalline MDMA, which is consumed in Australia, some countries in Europe, and in North America.

**Methamphetamine tablets** (“yaba”) has a form of small tablets of low purity that are available in different shapes and colours, commonly ingested or smoked after being crushed. They are frequently consumed in East and South East Asia. The specific content of methamphetamine tablets sold and used is unknown. They are not likely to contain purely methamphetamine, but it is likely to be a blend of amphetamine, methamphetamine, and other substances. Methamphetamine is also commonly used in West Asia and in Africa.

**Crystalline methamphetamine** (“crystal meth”, “ice”, “shabu”) is usually of higher purity and is commonly smoked, injected or ingested through nasal insufflation and commonly used in South East Asia and in Australia.

## **STIMULANT NEW PSYCHOACTIVE SUBSTANCES (NPS)**

The emergence of NPS has become a global issue since 2009. Among the different NPS reported to UNODC Early Warning Advisory, synthetic NPS that are stimulants comprise one third of such group of substance and include synthetic cathinones, piperazines, and phenethylamines.

## Treatment of psychostimulant use disorder

Only one in six people suffering from substance use disorders received treatment for those disorders during 2016, which is a relatively low proportion that has remained constant in recent years. Even though the prevalence of psychostimulant use at the global level is high, the proportion of individuals affected by PSUD who are seeking treatment is extremely low as compared to individuals with opioid use disorders seeking treatment. One of the reasons for low rates of treatment engagement of individuals with PSUD, in contrast to individuals with opioid use disorder is the absence of the medical model of treatment that includes medication in combination with psychosocial interventions, social support, other medical and social services, and behavioral incentives to attract and maintain engagement with treatment.

Globally the proportion of people provided treatment for psychostimulants use disorders also varies considerably and is also indicative of the main psychostimulant of concern in the region (Table 2).

**Table 2.** Proportion of people with psychostimulant disorders treated within treatment settings in each region

Regions	Cocaine	Methamphetamine	Amphetamine	Ecstasy
Africa	3%	33%	25%	0.10%
North America	13%	13%		
Latin America and the Caribbean	33%		0.4	0.4%
East and South East Asia	1%	60%	5.7	1.3
Western and Central Europe	10%	6.70%	4.40%	1
Eastern Europe and South Eastern Europe	4%	1%	2%	

Cocaine is a major drug of concern among those receiving treatment in Latin America and the Caribbean, where one third of those in treatment for substance use disorders are being treated for cocaine use, although that proportion has been declining. Cocaine use disorders are also reported as the primary reason for treatment, albeit to a lesser extent, in North America and Western and Central Europe. In North America, treatment primarily for cocaine use disorders has been declining in relative importance, due to the increase in the proportion of those in treatment for opioid use disorders.

Due to very limited ability of healthcare setting to engage patients with PSUD in treatment and limited benefits of available treatment programs many governments and organizations began to focus on development of new models of treatment that would incorporate evidence-based pharmacological and psychosocial interventions.

## STIMULANT USE: MEDICAL AND BEHAVIORAL CONSEQUENCES

### Stimulants: Mechanism of Action

All stimulants, both plant-derived and synthetic, increase the activity of monoamine neurotransmitters in the central nervous system; dopamine, noradrenaline and serotonin. Different pharmacological mechanisms are involved in the action of cocaine (inhibition of monoamine transport) and amphetamines (increased release of monoamines and reverse transport) but the net effect is similar for all substances. Understanding the exact pharmacological mechanism of these substances, as well as changes in the brain neurochemistry in individuals with PSUD, may help in development of medications to normalize those changes (Stoops and Rush, 2013).

Brain-imaging methods show that administration of stimulants produces changes in the activity in dopamine-rich areas of the brain suggesting the increase in the amount of dopamine. This increase in dopamine is associated with euphoria or pleasure reported by individuals using stimulants. This may change with the repeated administration of amphetamines, and/or severe stress, as dopamine-containing neurons become more sensitive and as a consequence, additional stress and amphetamine intake may cause greater release of dopamine release. This phenomenon of sensitization is thought to contribute to the development of psychotic symptoms and recurrent psychotic episodes in chronic users of stimulants.

Stimulants also increase the functioning of the noradrenergic system which leads to increase of heart rate and alertness causing user to feel energized and excited. While stimulants directly increase dopamine-related activity in the brain reward system, other drugs of abuse, such as opioids, cannabis, alcohol or nicotine, also produce increase in dopamine but often do so indirectly by first activating other receptors (e.g., opioid, cannabinoid or nicotinic).

Typically, the reported euphoria starts as the drug enters the brain and disappears as the drug leaves the brain. How fast the drug reaches the brain depends on how it is taken. Inhaled cocaine or methamphetamine vapor or smoke can deliver these substances to the brain in less than 10 seconds, with the peak drug concentration and the intensity of euphoria occurring within few minutes after taking it. Similar rapid onset and peak effect is seen after injecting the drug dissolved in the water into the vein. Drugs that are taken by inhalation of the dry powdered substance through the nose (also called insufflation, snorting, or sniffing), by rubbing it onto the gums, or oral ingestion (swallowing) take longer to be absorbed and make it way to the brain, with the euphoria starting after 15-45 minutes. These methods of use also result in the weaker but longer-lasting peak effect as compared to the inhaled drug vapor or smoke or drug injection. In general, the effect of a single dose of methamphetamine last longer than the effect of cocaine.

## Stimulants: Use Patterns and Effects

Daily patterns of stimulant use or intake can vary between individuals and in a given individual. Some may use small amounts on most days without escalation over time, while others may start using frequently and then progressively use larger amounts over longer periods of time. A common way that cocaine and amphetamines are used is in a binge pattern, when the drugs are used occasionally, for example, once to twice per month, but they are used repeatedly over many hours or days, and cumulatively in large doses. Stimulants are also used in combination with other drugs, most frequently alcohol, but also sedatives and heroin, either taken at the same time seeking experience of a combined drug effects, or sequentially to counteract the negative effects of the stimulant that may include anxiety, agitation, or paranoia.

### IMMEDIATE AND SHORT-TERM EFFECTS

As the name implies, the substances in this group stimulate the central nervous system. The intensity and duration of the immediate effects depends on the type and the dose of the substance and vary between individuals. Immediate effects include euphoria, rush, and burst of energy, which is usually a positive and pleasurable experience. Individuals who use stimulants typically report that they are more alert and less tired, have less need for sleep, and lowered appetite (Cruickshank and Dyer, 2009). Some individuals also report improved concentration and cognitive capabilities, sexual performance, and physical stamina which are often reported as reasons for continuing use of stimulants. The effect is more pronounced in individuals who may be tired, or sleep deprived as compared to those who feel well before taking the drug. Stimulants like MDMA may produce feelings of empathy, emotional openness and intimacy, and sensory changes, in addition to other stimulant effects.

Users of short-acting stimulants such as cocaine, who use it several times in a row, may rapidly develop tolerance to positive effects of the drug and feel a diminishing effect with each dose, which can lead them to take higher and higher doses. Additionally, with higher and repeated doses, the effect of stimulants may become less positive or desirable and may include anxiety, irritability, and overall unpleasant mood. Individuals can become restless or agitated, hypervigilant, aggressive, suspicious, and may develop psychotic symptoms such as paranoid delusions and hallucinations. Very high doses can produce stimulant delirium, a state with confusion and disorientation with severe anxiety.

In addition to psychological symptoms and changes in behavior, intoxication with stimulants can also produce physical symptoms including enlarged pupils, increased heart rate and blood pressure, chest pain or irregular heartbeat, nausea and vomiting, increased body temperature, excessive sweating or chills, abnormal movements, seizures, stroke, coma, and death. In overdose, unless there is medical intervention, high fever, convulsions, and cardiovascular collapse may precede death. Because accidental death is partially due to the effects of stimulants on the body's

cardiovascular and temperature-regulating systems, physical activities, and excessive exercise may increase the hazards of stimulant use.

## **LONG-TERM EFFECTS**

Use of stimulants over the extended period of time can lead to a variety of additional psychological symptoms as well as adverse behavioral and physical changes. Long term effect of stimulants use may include development of tolerance (diminished effects) and withdrawal symptoms when abstaining from the use. It may also result in various medical, psychiatric, neurologic and neurocognitive effects (Darke *et al.*, 2008, Scott *et al.*, 2007). Chronic use of stimulants frequently leads to the development of a (psycho)stimulant use disorder (PSUD), which has also been referred to as stimulant dependence or addiction.

### ***Stimulant Withdrawal***

When people with chronic stimulant use stop abruptly the stimulant that may experience symptoms of withdrawal. Stimulant withdrawal symptoms may include severe fatigue and sleepiness, depressed mood, at times accompanied by suicidal thoughts, and occasionally an increased appetite. These symptoms most often start within 24 hours of the last dose, earlier in users of cocaine than methamphetamine, with the most severe symptoms commonly lasting 1-3 days. This may be followed by less severe symptoms, lasting additional 1-3 weeks, and including low energy and motivation, anxiety, drug craving, depressed mood, difficulty with concentration, and sensitivity to touch (McGregor *et al.*, 2005). Sleep remains very disrupted with periods of sleeplessness or sleepiness, and lucid dreams. The withdrawal symptoms can be very unpleasant but are not inherently dangerous except in patients who become suicidal.

### ***Psychiatric complications***

Changes in mood (mania or depression) and anxiety are common in people with chronic stimulant use. When the severity and duration of these symptoms is greater than usually seen during intoxication or withdrawal, these syndromes are diagnosed as stimulant-induced mood or anxiety disorders.

Similarly, brief periods of paranoid thinking are common during stimulant intoxication, but when these symptoms persist for many days after the episode of cocaine or methamphetamine use, and include symptoms rarely seen during intoxication such as hallucinations and complex delusions, a stimulant-induced psychotic disorder can be diagnosed. Stimulant-induced psychosis is seen more frequently in people with chronic amphetamine use as compared to those with cocaine. Stimulant-induced psychosis resembles paranoid schizophrenia and while most of the time symptoms resolve during abstinence, 5-15 per cent of users fail to recover completely (Shoptaw *et al.*, 2009b). Other psychiatric complications may include compulsive sexual behavior (Dolatshahi *et al.*, 2016).

Stimulant use disorders frequently co-occur with other major mental comorbidities such as schizophrenia, major depression, post-traumatic stress disorder (PTSD) or attention deficit hyperactivity disorder (ADHD). Other substance use disorders may also co-occur, most commonly alcohol and opioid use disorder. Diagnosis of other co-occurring psychiatric disorders in patients actively using stimulants is very difficult as stimulant intoxication and withdrawal may mimic symptoms of other psychiatric disorders.



### ***Neurological complications***

Animal studies have documented that amphetamines, especially methamphetamine, have a toxic effect on the nerve cells, primarily affecting the dopamine system. Chronic use of stimulants has been associated with the development of cognitive impairment, presumably secondary due to neuroinflammation and disruption of blood-brain barrier chronic as well as constriction of blood vessels and deficiency in blood supply to the brain (Harro, 2015). Individuals with a history of amphetamine use may be more susceptible to developing neurodegenerative disorders such as Parkinson's disease. Some, but not all of these changes may resolve during prolonged abstinence. Abnormal movements in chronic users of stimulants can be seen and these may persist even after the use has stopped. Changes in the structure of brain have been detected in chronic stimulant users to persist for longer than a year even after stopping stimulant use.

### ***Other medical complications***

Other possible medical complications from stimulant use include severe dental problems, including cracked teeth from extreme jaw clenching when intoxicated and severe tooth decay; severe allergic reactions at injection sites as well as heart infections from injecting methamphetamine (Wright *et al.*, 2018); serious respiratory complications, including pneumonia, haemorrhage and respiratory failure from smoking, and other lung diseases; facial and body sores from scratching, sometimes leading to infections; extreme weight loss and starvation; sexually transmitted diseases sexual problems, as well as kidney damage and liver damage.

People who use stimulants often take a depressant to decrease excessive stimulation or to sleep following a stimulant binge. This combination is associated with spasms of coronary arteries that can damage the heart or an abnormal growth of heart valve cells leading to their dysfunction.

When used by a pregnant woman, psychostimulants increase the risk of placental separation and haemorrhage, premature birth, birth defects (including cardiac defects, cleft palate and club foot), and foetal brain haemorrhage and stroke.

## Stimulant Use Disorder

A significant number of individuals who begin using stimulants recreationally or to enhance performance will develop a stimulant use disorder. Commonly, recreational use of stimulants escalates over time, with more frequent episodes of use, increasing amounts per episode, and changes in the route of administration to deliver faster effects such as injecting. For example, individuals, who already receive prescription stimulants, may take the medicines more often than it was prescribed, and for non-therapeutic reasons, such as to achieve euphoria, often crushing tablets and snorting it. Students who use prescription stimulants without medical supervision to increase their academic performance will take higher and higher doses noting that they cannot function without stimulants and are not able to control the use. As a result, individuals who developed the disorder suffer from impairment in other aspects of their health, relationships, social function, and may develop work, housing, and legal problems.

### ETIOLOGY

Stimulant use disorder is considered to be a complex health disorder affecting the brain because changes in the brain functioning and pathological behaviours develop in vulnerable individuals in response to drug exposure. A large number of scientific studies show that stimulant use disorder, similar to other substance use disorders, has many determinants contributing to its origin, progression, and remission. These include biological, psychological and environmental factors. It is not known why some individuals are able to continue occasional stimulant use, while others slowly or rapidly escalate use and develop signs and symptoms of a stimulant use disorder but the individual differences and the external factors play an important role.

Biological factors are hereditary, genetically determined responses of the brain to stimulants including the development of long-lasting biochemical and physical changes in brain networks responsible for some of the symptoms of the disorder. A family history of depression or other mood disorders increases the risk for developing substance use disorder. Individual genetic risk factors may also play a role in development of substance use disorders.

Exposure to drugs early in life can alter brain development and increase risk of developing drug-related problems. Psychological factors, such as learning abilities, skills to cope with stress, sexual preferences and the ability to form new friendships, may influence the risk for developing drug-related problems and the ability to overcome challenges related to the symptoms.

Preexisting mental health comorbidities such as depression, bipolar disorder, anxiety disorder, PTSD and traumatic experiences, ADHD, learning disabilities, and personality disorders also increase the risk. The relationship between psychiatric disorders and substance use disorders is complex, with several mechanisms postulated. For example, individuals with chronic depression or other mood disorders may turn to stimulants to improve their mood and eventually losing their desire and ability to stop using the substance. However, use of substances may also increase the

risk for developing psychiatric disorders by directly affecting brain functioning, increasing the exposure to stress and trauma, or decreasing the ability to develop strategies to cope with stress.

Similarly, social environmental factors such as early life experiences, peer group, poverty, exposure to violence, or employment opportunities will modulate the emergence of the symptoms and the impact of the symptoms on the life of affected individual. The social and environmental factors can modify the response to the drug by changing the genetically determined brain responses (epigenetics).

A unique combination of these factors, each playing greater or smaller role in a given individual, impacts the onset, progression and the remission of the disorder. However, the dominant feature of the stimulant use disorder are the changes in the functioning of the brain and related behaviours. Scientific studies documented changes in the brain that occur and progress during the exposure to stimulants and gradually produce disruption of several areas of the brain which in turn can be linked to the symptoms of the disorder (Volkow and Boyle, 2018). For example, brain changes associated with increased craving and drug seeking, robust memories of drug effects, reduced ability to experience pleasure from activities other than drug use, increased activation of brain stress centres, impaired ability to resist unwanted impulses and make desired decisions.

## **STIMULANT USE DISORDER AS A CHRONIC HEALTH DISORDER AFFECTING THE BRAIN**

Stimulant use disorder is considered a chronic disorder because the abnormal brain functioning, and related symptoms persist for a long time. In its more severe form, PSUD persists for many years, with periods of worsening and improvement. Changes in the brain functioning of individuals with stimulant use disorder persist for a long time, even after the person is no longer using drugs (Stock *et al.*, 2019, Volkow *et al.*, 2001). These changes are responsible for the high rates of relapse and the recurrence of symptoms. It is not known whether these changes in the brain function can be reversed and the normal functioning restored.

In that respect, stimulant use disorder shares a lot of similarities with many other chronic disorders affecting other organs such as hypertension or diabetes. All of these disorders have genetic and environmental factors that contribute to the development of the disorder, have a chronic course with periods of symptom improvement and exacerbation. Medical and behavioral treatments, including interventions helping to abstain from certain foods and substances, play an important role in the management of all these disorders, though patients may have difficulty adhering to prescribed treatments. Therefore, stimulant use disorder is similar to many other chronic disorders of other organs.

Despite being a major and potentially devastating disorder, remission of stimulant use disorder symptoms is possible, and the individual can live a healthy and satisfactory life free of drugs. While some can recover without treatment, or with minimal or non-specific interventions, this mainly



happens in individuals with mild or moderate severity of substance use disorder. People with the severe form of the disorder rarely recover without specialized treatment.

Stimulant use disorders are best addressed in the healthcare treatment settings. Best evidence supports treatment using pharmacological treatments supplemented by psychosocial and other non-pharmacological interventions. This is the same approach that is used in treatment of other chronic medical and psychiatric disorders.

## EVALUATION AND DIAGNOSIS

Stimulant related disorders can be diagnosed based on the results of medical and psychiatric evaluation in individuals who report using stimulants and developing related problems. Confirming the self-reported stimulant and other substance use using urine or blood testing is an essential component of the evaluation.

Each of the two main diagnostic classification systems, ICD-10 and DSM-5, defines the specific criteria that have to be met in order to make a diagnosis (see Appendix). Broadly speaking, the stimulant use disorder, commonly referred to as stimulant dependence or addiction, is diagnosed when the stimulant use leads to a significant impairment of functioning or a distress during the past year.

DSM-5 defines a **Stimulant Use Disorder** when at least two of the eleven diagnostic criteria are met. In ICD-10 the primary use disorder is **Stimulant Dependence**, which can be made if the individual has met at least three of the six possible criteria. Some of the criteria, which overlap for both diagnostic systems, include:

- the strong desire to use the stimulant and inability to control or stop the use
- persistent preoccupation with obtaining and using the stimulant even though the use interferes with daily activities and causes problems
- increased tolerance to the immediate effects of stimulants
- signs of physical withdrawal on abrupt stopping of the drug that has been used chronically

Other stimulant-related psychiatric disorders can also be diagnosed:

- **Stimulant Intoxication** is diagnosed when stimulant use causes clinically significant problematic behavior, psychological or physical change such as hypervigilance, paranoid ideations, agitation, abnormal heart rate, or seizures.
- **Stimulant Withdrawal** is diagnosed when stopping prolonged use of a stimulant results in feelings of depression and dysphoria and physical symptoms such as psychomotor slowing, excessive tiredness and sleepiness, or increased appetite.

If possible, a physical exam, a comprehensive blood examination, urine analysis, electrocardiogram, as well as tests for infectious disorders (HIV, hepatitis, TB and STIs) allows for a diagnosis of frequently co-occurring medical disorders.

## TREATMENT

### Treatment Setting

Use of stimulants and progression to PSUD occurs on the continuum of severity of symptoms and related problems, from the use of prescription stimulant medication inconsistent with the prescription to the severe PSUD with psychiatric and medical complications. Similarly, interventions designed to minimize the negative impact of stimulant use can occur alongside a continuum of treatment settings (less or more medical supervision) and the intensity of interventions matching the needs of individuals. The severity of presenting problems usually determines the most appropriate treatment setting.

Outside of the formal treatment setting, harms related to stimulant use can be minimized using community-based, low-threshold, outreach interventions, which are directed at individuals who are not motivated for the recovery process. Use of prescription stimulants not consistent with the prescription and without medical monitoring can be addressed using risk-reduction strategies.

Acute intoxication, withdrawal, and stimulant-induced psychiatric disorders can be treated at the psychiatric or toxicology inpatient units while medical complications can be treated in the general medical units. Individuals with PSUD are traditionally treated in a specialty, addiction-treatment programs, both residential and outpatient, which are often separate from the mainstream healthcare setting.

With the growing understanding of PSUD as a chronic health disorder, and the increasing availability of medical treatments, it is acceptable to provide treatment in the public health system, in parallel to the treatment of other chronic psychiatric and medical disorders. The general medical setting may be appropriate for treatment of individuals with mild or moderate severity disorder while those with severe disorders should be treated in the specialty in addiction treatment setting. Ideally, an addiction medicine specialist should be available for consultation to non-specialist medical providers in the general public health system. Moreover, medical settings may be more appropriate for identifying and treating individuals with early stages of the disorder with a goal to prevent its escalation, which is the most effective way to manage the disorder. Patients with more severe or complicated PSUD can be referred to specialized treatment programs.

Many individuals with stimulant use problems or PSUD do not seek help. They may not be aware that these problems may be addressed in the treatment program, that such programs may be available, or may not recognize their stimulant use to be a problem. Other reasons include embarrassment or stigma, belief that treatment is not necessary, and privacy concerns (Cumming *et al.*, 2016). Consequently, the rates of treatment seeking among them are generally low. The comparably low rates of treatment seeking may also be driven by the perception that medical or medication-based interventions for treatment of PSUD are generally not highly efficacious. Individuals with stimulant use problems who enter treatment programs often do so in response to

external factors or motivators, insistence or pressure from family members, work or profession related requirements, or legal enforcement. While it is sometimes debated in literature, whether self-driven or internally motivated treatment initiation is the most desirable and may lead to better outcomes, the scientific evidence accumulated to date does not support such claims. Individuals entering treatment for stimulant use disorder could benefit from provided interventions regardless of their initial reason for treatment initiation. Treatments that are accessible, attractive, and patient-centred, are able to retain patients for extended periods of time can provide useful therapeutic interventions to a broad range of individuals needing treatment.

## Treatment Interventions and Goals

Stimulant-related disorders can be effectively treated using a range of pharmacological and psychosocial interventions. These interventions have been developed with the support of scientific evidence and their effectiveness have been tested using scientific standards used in developing treatments for other medical disorders. Several evidence-based psychosocial interventions have been developed and can be implemented in community-based treatment programs. A range of pharmacological interventions have also been evaluated and are in clinical use. None of the pharmacological interventions have been however officially approved by regulatory agencies for the treatment of PSUD.

The goals of PSUD treatment are similar to goals of treatment of other chronic disorders. The primary goal is the remission of symptoms of the disorder, as defined by the diagnostic criteria. This primarily involves the reduction or cessation of drug consumption, with improvement in physical and psychological health and improvement in functioning. The ultimate goal of treatment is to maintain long-term and stable remission of symptoms to prevent future harms.



## Psychosocial treatment interventions: Evidence-Based Treatments

It is generally recognized, that most individuals who experience stimulant use problems or may have stimulant use disorder are not seeking medical treatment or professional services. Among the minority who seek some form of help to overcome their stimulant use problems, the most common type of interventions available is peer-based counselling and support programs. These interventions are often based on the principles of 12-step recovery programs called Alcoholics or Narcotics Anonymous (AA/NA). The effectiveness of such programs for helping to overcome stimulant use disorders have not been extensively evaluated in controlled clinical trials and prevalently mixed evidence based on individual narratives exist. While scientific evidence in

support for stand-alone peer-based interventions and support programs is not strong, such programs have the capacity of providing additional, useful, and potentially effective recovery support for some individuals enrolled in formal treatment programs. In such complementary role, peer-based interventions and support programs could be recommended to individuals with stimulant use problems or PSUD on as needed or desired basis.

Among various psychosocial interventions that have been evaluated in controlled clinical trials contingency management (CM) and cognitive-behavioral therapy (CBT) have been consistently found to be efficacious for PSUD (De Giorgi *et al.*, 2018b, Dutra *et al.*, 2008, Lee and Rawson, 2008, Lussier *et al.*, 2006, Minozzi *et al.*, 2016, Prendergast *et al.*, 2006). Evidence from clinical trials of other interventions, including various forms of motivational enhancement therapies (MET) (Carroll and Onken, 2005, Lundahl *et al.*, 2010, Smedslund *et al.*, 2011) and a broad spectrum of interventions under the umbrella term of “drug counselling” still need to be systematically evaluated (Ferri *et al.*, 2006).

## **CONTINGENCY MANAGEMENT**

Contingency Management (CM) is an intervention aimed to eliminate or change specific behaviours that are closely related to substance use by utilizing positive reinforcement procedures, or rewards. CM is based on principles of operant/instrumental conditioning developed by Skinner showing that over time, behaviours that are rewarded are likely to increase. Additional theoretical foundations of CM include models and theories of goal-directed behaviours, reward learning and motivational control models.

In a typical implementation of CM for treatment of PSUD, the patient receives a reward (monetary, or through other tangible and valuable tokens) that is contingent upon the reduction of substance use documented by providing a biological sample (often urine sample) that is negative for tested drugs. Many high-quality studies provide strong evidence that CM is efficacious in reducing substance use or maintaining initial abstinence during treatment when rewarding contingencies are actively provided. However, research evidence also suggests that when individuals are no longer subject to contingencies, the magnitude of the treatment effects may decline (Benishek *et al.*, 2014).

Despite extensive supportive scientific evidence of efficacy, CM has received a limited acceptance worldwide. It has been disseminated in a limited number of real-world implementations in the US and other Western countries (Petry, 2011), but in other cultural contexts CM is seen as controversial. Some reasons for the lack of a broader acceptance stems from the fact that providing monetary or other rewards to people who engage in illegal or socially unacceptable behaviours is not acceptable in many social and cultural contexts. Additionally, the underlying science of operant conditioning is seen as complex and selection of types and schedules of reinforcements, rewards, and punishments may strongly influence the overall treatment outcomes.

For example, it has been demonstrated in laboratory settings that immediacy of reinforcement, or rewards is important. However, in real-world clinical settings this principle is difficult to implement as urine test result is temporarily distant from the substance use event. In principle, only individual therapy applications of CM interventions are possible, also diminishing somewhat the appeal of this type of intervention in some clinical settings.

Despite limitations and implementation challenges, CM based treatment interventions may improve patient engagement in recovery efforts and facilitate achievement of initial important recovery goals, including reduction of substance use or initial abstinence. Practical, real-world implementations of CM based treatment interventions can utilize a broad range of monetary and non-monetary rewards linked to either urine toxicology screen results, treatment participation behaviours (e.g., clinic attendance), other critical recovery activities or markers (e.g., medication adherence), or behavioral changes linked to successful recovery. CM interventions are typically non-conflicting with therapeutic principles of medical or other psychosocial treatments and can enhance the overall treatment efficacy. They can be used intermittently, repeatedly, or as needed, to intervene with selected aspects of the larger goals of treatment participation and/or to prolong successful recovery (Vocci and Montoya, 2009).

Extensions of CM based interventions that may include a broad range of larger scale motivational incentives linked to successful achievement of predefined recovery goals. For example, help for housing, access to jobs/vocational trainings, or other forms of rewards or support may be given contingent on abstinence or treatment participation (McPherson *et al.*, 2018). Overall, while such extensions or modifications of CM are supported by theoretical principles of behavior modification by rewarding desirable outcomes, the existing evidence based on published research on potential efficacy is not extensive or strong.

## **COGNITIVE BEHAVIORAL THERAPY**

Cognitive Behavioral Therapy (CBT) is an umbrella term for a range of psychosocial interventions that are considered cognitive and/or behavioral in nature. In general, CBT for substance use disorders focuses on examining the relationships between thoughts, feelings and behaviors related to substance use and recovery. During CBT patterns of thinking that lead to substance use and the beliefs that direct these thoughts are explored, and the treatment interventions aim to modify those negative or destructive patterns of thinking to improve coping skills (Beck *et al.*, 1993). Often, in addition to specific verbal CBT communication techniques delivered by the CBT therapists during treatment sessions with patients, practical exercises in real-life environment outside the treatment venue and patient self-guided activities (e.g., keeping thought logs) are also prescribed. The overall aim of CBT is to help patients to understand negative thinking and to develop healthier thinking and improved coping skills which can be incorporated it into their lives (Carroll and Onken, 2005).

Typical implementations of CBT for treatment of PSUD often include a combination of various psychosocial interventions. For example, CBT can include educational, didactic, and skills learning components targeting cognitive functioning (i.e., thinking, memory, decision making), as well as components directed at emotional/psychological functioning related to substance use problems and recovery. CBT for PSUD often includes or is combined with other interventions, such as relapse prevention, motivational enhancement, contingency management, couples and family interventions.

CBT has a broad clinical appeal and can be administered in both individual and group formats, and in face-to-face (human-to-human) or technology based/supported settings (McHugh *et al.*, 2010).

Overall there is a small to moderate scientific evidence (in terms of observed effect sizes in controlled clinical trials) supporting therapeutic efficacy of CBT-type interventions as compared to other interventions for treatment of PSUD. Only a relatively small number of studies with high scientific quality has been published. CBT implementations that were studied, included a very broad spectrum of interventions, settings, and participant populations. Additionally, CBT has been typically tested against low strength of evidence comparators (e.g., treatment as usual, wait-list control) and only showed a limited efficacy, with some studies demonstrating mixed results. CBT for substance use disorder is typically implemented as a fixed duration intervention (e.g., 3- or 6-month duration in typical clinical trials) and the observed beneficial effects tend to diminish after treatment discontinuation (Butler *et al.*, 2006, Lee and Rawson, 2008, Minozzi *et al.*, 2016).

Practical, real-world implementations of CBT based interventions for stimulant use disorder can vary in specific implementation details depending on clinical contexts or specific local settings. Typically, a CBT based intervention includes a series of scheduled appointments with either fixed (e.g., once per week) or varied frequency (e.g., more frequent than once per week during the initial phases of treatment, with diminishing frequency in later phases of treatment). Session duration can vary from a very short (e.g., 10 min) to much longer (e.g., 90 min) depending on specific session goals, treatment progress, or specific therapeutic circumstances. Both face-to-face and technology supported contacts between the patient and the interventionist could be considered, based on the patient progress or needs, program context and resources, factors limiting or facilitating access (e.g., available transportation, distance, cost), or intervention goals. CBT sessions can be offered in individual or group format, or they can include some mixture of both formats (McHugh *et al.*, 2010).

CBT interventions are delivered by trained psychotherapists or counsellors. Depending on local regulatory contexts, CBT could be provided by individuals without advanced degree or specific professional psychotherapy or counselling certification. However, the effectiveness of CBT interventions tends to be higher when provided by therapists with good general counselling background and extensive practical experience who also received CBT specific training and ongoing clinical supervision. A relatively low number of trained CBT therapists limits the reach of this method of treatment, particularly in developing countries.

CBT therapists typically follow an explicit treatment plan based on the overall treatment goals and the specific patient needs, rather than providing unspecified support, ad hoc interventions addressing current, emerging situations, or problem solving based on immediate, transient patient related context.

CBT based interventions are often manualized and are offered following closely the manual guidelines regarding the frequency and format of therapeutic contacts, the length and content of specific sessions, the overall duration of treatment, the use of specific techniques or communication styles, and other treatment details. While CBT interventions are typically not open ended, with predefined duration and goals, each patient can receive multiple episodes of the intervention if needed.

Even manualized CBT interventions are not rigid. They allow and often instruct treatment providers on ways to individualize the course of treatment based on patient progress, needs, and specific circumstances (Dobson, 2001). Various extensions of standard/typical CBT based interventions for treatments of substance use disorder have been used to address important, patient specific recovery contexts. For example, family involvement in the patient recovery process can be addressed by providing additional family session as a part of the overall treatment plan.

## **MOTIVATIONAL ENHANCEMENT THERAPIES/MOTIVATIONAL INTERVIEWING**

The general aim of Motivational Enhancement Therapies (MET) is to strengthen or enhance the internal motivation for health-related change such as reduction or elimination of substance use, or treatment initiation. MET for PSUD is often implemented as a form of Motivational Interviewing (MI) (Miller and Rollnick, 2002). MI is primarily a talk therapy (sometimes called “collaborative conversation”) focused on exploring and positively resolving patient’s ambivalence about substance use or recovery initiation. Briefly, during MET/MI the clinician, using specialized communication skills, elicits the patient’s own reasons and rationale for possible changes, referred to as “change talk.” It is often assumed that once the ambivalence about changing the behaviour is resolved, the patient can often engage and continue recovery on their own. Therefore, MI can include a process of planning for and activating changes, by engaging in a formal treatment intervention. In general, MET/MI is focused more on discussing the “whether” and “why” to change rather than the “how” to change (Rohsenow *et al.*, 2004).

MET/MI type psychosocial interventions have been extensively evaluated for alcohol use disorders and to a lesser extent for marijuana or cocaine use disorder. There is some evidence that MET/MI can be efficacious for treatment of PSUD as compared to no intervention, but the overall quality of evidence of MET/MI efficacy is low (Smedslund *et al.*, 2011).

Clinically implemented MET/MI interventions are often brief (1-4 sessions). It is broadly accepted that MET/MI is particularly useful in engaging patients in discussing their problems and potential treatment needs and in initiating treatment. Some challenges and criticisms of these type



of interventions stem from the fact that in order to be highly effective, MET/MI specific techniques and communication style requires practice and mastery of skills through specific training, practical experience, and supervision.

Real-world implementations of MET/MI based interventions for PSUD can also vary considerably in specific implementation details depending on clinical contexts or specific local settings. However, the overall focus of MET/MI based interventions is typically narrowed to address primarily or exclusively the patient's motivational states, and the most often prescribed and practiced interventions are based on MET/MI specific communication style and techniques. In specific, local clinical contexts, both the local language and local communication norms may pose challenges to effectively implementing MET/MI. Nonetheless, MET/MI based interventions have been embraced by the international communities in many clinical contexts. Drawing on the shared collective experiences of the international MET/MI community, it is likely that the general principles of MET/MI could be effectively implemented in most clinical contexts, and the resulting interventions could be effective in a broad range of clinical contexts. MET/MI is typically provided by therapists who received extensive specialty training regarding the treatment principles and specific communication techniques (Martino *et al.*, 2008).

## **OTHER PSYCHOSOCIAL TREATMENTS FOR PSUD DISORDERS**

### ***Drug Counselling***

Drug counselling, primarily provided in outpatient settings, is the most available and most often used intervention. However, this type of intervention has not been extensively evaluated in controlled clinical trials, and currently there is no evidence of efficacy of such interventions for treatment of PSUD. Drug counselling is a very broad term to describe individual or group psychosocial interventions that aim to help patients reduce or eliminate substance use. Drug counselling implemented in clinical settings typically includes an educational component and may incorporate elements of cognitive, behavioral, and supportive psychotherapies. Drug Counselling



interventions have been shown to be moderately effective for other substance use disorders, especially when combined with medications (De Giorgi *et al.*, 2018a, Minozzi *et al.*, 2016). A similar comprehensive approach, of combining medications with various psychosocial interventions, even if the individual components of the comprehensive approach are not strongly efficacious, should be considered for treatment of PSUD.

### ***Educational Interventions***

Potentially useful psychosocial components may include competently offered educational interventions. Purely educational interventions (often called “psychoeducation”) have not been extensively evaluated as stand-alone treatments, and sometimes they have been included in research as placebo-like comparators in published clinical trials. However, many effective interventions for substance use disorders (e.g., CBT-based) include extensive educational components. Educational or didactic intervention can help patients to understand the underlying factors of substance use problems, to learn about available effective treatment and recovery options and strategies, and to set realistic expectations regarding the recovery process. Behavioural aspects of the PSUD development and the effective recovery process need to be emphasized during educational interventions. Didactic components of effective psychosocial interventions should inform the patient about immediate and long-term responses of the central nervous system to stimulants, that stimulant use disorder is a condition resulting from dysregulation of important brain functions and learned/acquired skills, and about maladaptive habits and behaviours that typically develop during prolonged and repeated substance use. Other didactic components should provide accurate, science-based information about how psychoactive substances interfere with the fundamental functions of the nervous system resulting in both pleasurable or desirable, as well as unpleasant or harmful effects. Education about effective recovery strategies within a medical treatment model that are similar to effective recovery from or successful management of chronic medical conditions, such as diabetes, asthma, cardiovascular, allergy, hormonal, or other where supportive use of medications and lifestyle changes are most effective, should also be included.

Effective educational interventions utilize communication style and techniques that maximize the patient understanding and acceptance of provided information. Language and all supportive teaching materials (e.g., visual illustrations, examples, narratives, etc.) must match the educational level and experiences of the patient. Interactive teaching and learning styles and methods where both the educator and the student interact, share information, ask and answer questions, provide clarifications and examples closely relevant to the experiences of the learner are generally more effective than a passive reception of prepared content (lectures). Paraphrasing, summarising, and balanced repetition of material throughout the course of the intervention is generally most effective.

Educational interventions can be delivered by trained counsellor who have general qualifications required to provide drug counselling and who are trained in effective delivery of educational content and materials. Educational components are generally also highly suitable to be included within CBT based or supportive drug counselling. They can be useful components of peer-based interventions and can supplement, as separate components, interventions based on the principles of CM or MET/MI.

## PRINCIPLES FOR EFFECTIVE PSYCHOSOCIAL TREATMENT

Psychosocial interventions provided as standalone treatment or as a part of a more comprehensive approach that combines them with medications or medically based interventions should adhere to a set of principles that have been shown efficacious and effective in other treatment settings. Principles of effective treatment interventions that have demonstrated beneficial effects on the overall treatment outcomes in substance use disorders include the following recommendations:

- Minimize barriers to initiate and continue treatment.
- Provide a broad range of integrated therapeutic components, even if individually they are of low efficacy.
- Provide treatment interventions through general medical, primary care, or community healthcare settings engaging general medical practitioners, nursing or other medical and non-medical personnel who can be trained and supervised to provide good quality care to patients with substance use disorders.
- Recovery from substance use disorders is generally a long-term process, therefore it is important to maintain patient engagement regardless of perceived or measured treatment progress or lack of thereof. Many patients may require multiple attempts to engage in recovery and/or to maintain sustained recovery.
- Extended patient contact/engagement with healthcare intervention can reduce harms of substance use and can reduce risks and harms of substance use related comorbidities.
- Medical evaluation and medically based intervention can be very effective. Initial recovery in a hospital, inpatient, or a healthcare facility may be helpful. Taking medications may help to reduce substance withdrawal symptoms and prevent or protect against disruption of recovery efforts.
- Monitoring of treatment progress or for disease symptoms recurrence/worsening should be integral part of an effective treatment plan. Ongoing visits with medical professionals to monitor treatment progress and to adjust or change treatment are necessary.
- Successful recovery from substance use disorder involves important lifestyle changes including changing habits and activity levels and adopting a lifestyle supportive of prolonged recovery and avoiding situations that can increase likelihood of symptoms reoccurrence.
- Outpatient treatment with active involvement of the patient in his/her own treatment and recovery, involving practicing new skills in the real-life environment, while maintaining support from the family, friends, or society are generally most beneficial forms of recovery approaches.

## Pharmacological Treatment of Stimulant-related Disorders

Medications can be useful in the management of various clinical syndromes seen in individuals who use cocaine or amphetamines including: management of intoxication and withdrawal, treatment of stimulant-induced psychiatric disorders, and treatment of a stimulant use disorder (PSUD).

The current scientific model of stimulant-related disorders and the available evidence is summarized below. Results of randomized controlled clinical trials conducted in patients presenting for treatment are briefly summarized. When available, results of recent meta-analyses are also included. In the absence of such studies, the expert consensus on the pharmacological management of stimulant-related disorders is presented.

### MANAGEMENT OF STIMULANT INTOXICATION

Individuals with severe and complicated stimulant intoxication usually present in the acute distress in the emergency medical setting. The severity and duration of symptoms depend on the type of substance used and the dose, though the patient may not be able to provide many medical history details. Intoxication with cocaine or methamphetamine can include physical signs and psychiatric complaints. Patient may have unstable blood pressure and heart rhythm, may have chest pain and cardiac infarct, may have seizures, stroke, elevated body temperature (methamphetamine), disorientation, impaired consciousness, and abnormal body movements. Some of these symptoms can be severe and lead to death if not treated. Therefore, prompt diagnosis and stabilization using standard medical and pharmacological interventions is critical at this stage. As many individuals present to the emergency room with dehydration, ensuring adequate oral liquid intake should be implemented to restore electrolyte balance and reduce body temperature, which can complicate treatment if left untreated (Jenner, 2006). Hyperadrenergic state can be managed using betablockers to prevent acute coronary syndrome (Richards *et al.*, 2015).

The psychiatric and behavioral symptoms may include agitation and aggression, severe anxiety, irritability, and dysphoria, bizarre uncontrollable movements, mania, paranoid symptoms, and hallucinations. The risk of aggression is increased in individuals who also consume alcohol and have psychotic symptoms (McKetin *et al.*, 2014). The primary management of psychiatric symptoms include placing the patient in a quiet room with minimal stimulation, where a staff member can provide reassurance, support, and reorienting to the present situation, talking with the patient to help them focus on the breathing and physical sensations. Listening to the patient with empathy, acceptance, and understanding and the constant presence of the same staff member with minimal interruptions usually decreases many of the initial symptoms. This method is preferable to using sedative medications as the first-line treatment.

However, the behavioral intervention may not be sufficient in patients with severe symptoms of intoxication and symptom-focused pharmacological interventions may be necessary to decrease

the risk of harm to the patient and others. In patients with severe symptoms benzodiazepines, especially fast acting diazepam or lorazepam (given orally or with the intramuscular injection) are usually given as the first line of treatment (Richards *et al.*, 2015, Wodarz *et al.*, 2017).

In patients who have limited response peak to benzodiazepines, or in patients who present with psychotic symptoms, antipsychotic medications may be administered in addition to benzodiazepines. This includes typical antipsychotics such as haloperidol or atypical ones such as olanzapine or risperidone, and beta blockers like propranolol. The choice of the most appropriate medication to manage agitation will depend on the urgency, need for repeated treatment, and the potential side effects of medications (Jenner, 2006, Richards *et al.*, 2015).

As intoxication with stimulants increases the risk for seizures, benzodiazepines, which have anti-seizure effect, should be used before antipsychotics which increase the risk for seizures. Assuring appropriate hydration can decrease side effects of antipsychotic medications.

The acute intoxication usually resolves within the period of hours and therefore ongoing treatment with medications may not be necessary. However, patients need to be observed for emergence of symptoms of stimulant withdrawal or the persistence of psychiatric symptoms.

Treatment of stimulant withdrawal and the initial treatment of PSUD can occur on the inpatient medical unit, in the residential program, or on the outpatient basis. Some national guidelines (e.g., German and Australian) recommend an extended period of inpatient treatment with goals of assuring abstinence, conducting an extended observation and a thorough psychiatric and psychological evaluation, providing psychoeducation and treatment planning, and to initiate pharmacological and behavioral treatment. However, most of those goals can be accomplished on an outpatient basis as inpatient or residential treatment can be expensive and time limited and may not be available in many communities.

## **MANAGEMENT OF STIMULANT WITHDRAWAL**

### ***Acute withdrawal***

Withdrawal symptoms usually follow an episode of prolonged use of large doses of cocaine or methamphetamine. Symptoms of withdrawal can be so severe as to bring patients to the emergency room to seek care. The most prominent symptoms of withdrawal include severe depression and suicidal ideations but can also include anxiety, irritability, agitation, anhedonia, fatigue, disrupted sleep, and drug cravings (McGregor *et al.*, 2005).

As with the management of stimulant intoxication, intensive supportive behavioral intervention should be at the centre of the initial management of stimulant withdrawal. The acute symptoms can be quite severe, including intense suicidal ideations, but these are usually short-lasting and self-limiting. Patients with severe symptoms and/or suicidal ideations should be monitored and treated

in an inpatient setting to assure frequent monitoring for safety while providing support, reassurance, and psychoeducation about stimulant withdrawal.

The behavioral intervention may not be sufficient to fully relieve withdrawal symptoms and cravings, and persistent psychiatric symptoms put patients at risk of suicidal attempts or dropping out of treatment. In such situation, anxiety and agitation can be treated with benzodiazepines, although these are no controlled studies evaluating their effects and safety. In case of the psychotic symptoms that persist beyond the initial period of intoxication and cause distress patient may benefit from the antipsychotic medication, with atypical agents preferred over high potency agents. Atypical antipsychotics, such as olanzapine or quetiapine, can also be given for the short-term relief of severe agitation or insomnia that occurs during stimulant withdrawal.

In addition to symptomatic treatment with benzodiazepines, scientific studies evaluated the effect of other medications with the primary focus to relieve withdrawal and craving, as well as those that could reduce the risk of early relapse. The results of these studies were mixed, with no medication consistently showing added benefit during the first one to three weeks of treatment, which usually occurs in inpatient units (Pennay and Lee, 2011, Shoptaw *et al.*, 2009a).

Because depressed mood is often associated with stimulant withdrawal, antidepressant medications were evaluated for treatment of withdrawal but there is no consistent evidence that these medications are helpful (Pani *et al.*, 2011). Nevertheless, antidepressants are used to target depressive symptoms during early abstinence, with the dopaminergic antidepressant bupropion and noradrenergic antidepressant desipramine used most commonly. As insomnia may be a major symptom during early abstinence from stimulants, sedating antidepressants such as mirtazapine, doxepin, or trazodone may be offered. In case of severe insomnia, sedating antipsychotic medications may also be used for a short-time. There is no evidence to suggest use of neuroleptics to treat symptoms of uncomplicated stimulant withdrawal.

### ***Protracted withdrawal***

After the resolution of acute intoxication and withdrawal, patients who were stabilized on the inpatient unit are often discharged and continue treatment as outpatients. However, many of them continue to experience discomfort that is sometimes referred to as “protracted withdrawal.” It includes difficulties with memory and cognition, increased impulsivity and impaired decision-making, exaggerated response to drug-related environment (cues), depressed mood and mood lability, anhedonia, anxiety, and drug craving (McGregor *et al.*, 2005). The severity and duration of these symptoms vary greatly, but in some individuals, symptoms can last for many weeks after cessation of use, with periods of improvement and worsening. Eventually, these symptoms fully resolve in patients who are able to remain abstinent, however, this period is associated with a high risk for relapse, most likely due to the persistence and severity of these symptoms. Some of the interventions used, both pharmacological and behavioral, target symptoms persisting during early abstinence with a goal to extend the abstinence and prevent relapse.

It is proposed that symptoms encountered in patients in early abstinence may be associated with the decrease or “deficit,” in the functioning of the dopaminergic system. A medication that will “normalize” the functioning of the dopaminergic system may decrease craving and other symptoms of prolonged withdrawal and will minimize the risk for relapse (Volkow and Boyle, 2018). The strategy that had the most support to date involve the use of medications that enhance the dopaminergic neurotransmission counteracting the dopaminergic deficit. This strategy includes numerous cocaine and amphetamine analogues as medications and is often referred to as “agonist therapy” or “replacement therapy,” in parallel to methadone or buprenorphine treatment in opioid use disorder.

## **MANAGEMENT OF STIMULANT USE DISORDER**

The main mainstay of PSUD treatment takes place after the period when acute symptoms of intoxication and withdrawal resolve. It may occur during the period of residential treatment that follows an acute inpatient care or during the long-term outpatient treatment.

The primary goal of treatment is to help maintain benefits achieved during the initial phase of treatment, usually to maintain the abstinence from stimulants (relapse prevention) and to facilitate the resolution of PSUD symptoms (symptom remission). However, some patients who present for treatment did not receive inpatient treatment and continue using stimulants or relapse immediately after the inpatient discharge, and in such patients the main treatment goal would be to reduce and ultimately stop drug consumption (abstinence-induction), with improvement in physical and psychological health and improvement in functioning to prevent future harms. The ultimate goal of treatment is to maintain long-term and stable remission of symptoms.

At present, outpatient treatment programs rarely offer medical interventions to assist with abstinence-induction or relapse prevention, rather they offer psychosocial interventions of varying quality. This is in contrast to programs offering outpatient treatment for individuals with opioid use disorder, which involves medication maintenance with adjunctive psychosocial interventions. Therefore, many programs treating individuals with PSUD have difficulty attracting and retaining patients in treatment, whereas patients with opioid use disorder are more likely to enrol, remain, and benefit from treatment for much longer periods of time. It is possible that a model of PSUD treatment that involves long-term medication maintenance will be much more attractive and beneficial to individuals seeking help.

## **THE RATIONALE FOR PHARMACOLOGICAL TREATMENT**

It is postulated that in individuals genetically predisposed to develop stimulant use disorder, or exposed to environmental risk factors, repeated exposure to cocaine or amphetamine results in changes in the neural circuits and the functioning in various brain areas. This in turn leads to changes in behavior, mood, cognition, decision making, response to stress, and the ability to control impulses

which is characteristic of individuals with stimulant use disorder (Goldstein and Volkow, 2011). Changes in the functioning of the brain are responsible for both the inability to control or stop stimulant use and the increased risk of relapse during early stages of abstinence such as in people discharged from residential treatment programs. It is postulated that a treatment with medication will normalize some of the changes in brain functioning, decreasing impulsivity and craving for the drug, allowing individuals to decrease or stop drug use and to benefit from psychosocial treatments (Volkow and Boyle, 2018). This change can be gradual, which may be attractive to patients who are not ready or able to engage with drug treatment that requires complete abstinence at the outset.

Both cocaine and amphetamines increase the amount of the neurotransmitters dopamine and noradrenaline and over time produce long-lasting changes in brain circuits (Kalivas and O'Brien, 2008). Because of the well characterized biological mechanism of the disorder, a number of scientific studies were conducted in search of medications that could modify or reverse the brain changes responsible for the maintenance of stimulant use disorder and help affected individuals achieve and maintain abstinence from cocaine or amphetamine. Search for medications to treat cocaine or amphetamine use disorder has been also informed by the discoveries of medications that are effective in treatment of opioid, tobacco, and alcohol use disorders, but finding treatment for stimulant use disorder appears to be more complicated.

More than 100 various medications have been clinically tested over the past 30 years, yet there is no medication that was shown to have a large and reproducible beneficial effect and therefore no medication has been approved in any country with the indication to treat stimulant use disorder. However, in the last 5-10 years, several candidate medications, primarily from the class of prescription psychostimulants, were found to be effective in well-controlled treatment studies in patients with stimulant use disorder. As the number of studies is increasing, recently published systematic reviews and meta-analyses that combine results from several studies point to the emerging evidence of the benefits offered by psychostimulant medications (Castells *et al.*, 2016).



Psychostimulant medications have a pharmacological effect that is similar to the effect of drugs that the patient may be addicted to. The main difference is that psychostimulant medications are taken orally, on daily basis, providing consistent dopaminergic stimulation. Prescription psychostimulants produce minimal or no psychoactive effects as the medication is constantly present in the brain and patients usually develop tolerance to stimulant psychological and physical effects. This is very different from the effects of injected or smoked cocaine or methamphetamine, or irregularly swallowed or snorted high doses of oral stimulants, with large doses rapidly entering the brain causing the individual to experience extreme stimulation and euphoric effects. When



taken as prescribed, psychostimulants may have a normalizing effect, reversing the underlying deficits in the functioning of the dopaminergic system without further dysregulating the system. As a result, patients have less craving, have less impulsivity, and can abstain from illicit stimulants. In support of this approach, brain imaging studies showed that psychostimulant medications can normalize the function of the brain centres affected by the chronic exposure to stimulants and in turn diminish symptoms of the disorder (Zilverstand *et al.*, 2018).

The same pharmacological principle, sometimes referred to as a “replacement” or “substitution therapy,” is used in treatment of opioid dependence, where opioidergic medications methadone and buprenorphine eliminate withdrawal and craving helping to reduce or stop heroin use. Similarly, nicotine or a nicotine receptor agonist varenicline, medications that have pharmacological effects similar to the effects of tobacco, are useful in treatment of tobacco dependence.

In addition to providing relief of withdrawal and craving, psychostimulants medications may have mildly positive effects which will be an incentive for patients to come to the clinic for prescription or to have medication administered on-site. That way patients may be motivated and willing to accept additional behavioral and supportive interventions, participate in recovery-oriented activities, and seek additional medical and psychiatric care. This model is similar to clinic-based, long-term treatment with methadone or buprenorphine which includes supervised doses of the medication, with small number of take-home doses, in addition to all other medical and recovery services available on-site.

## **PSYCHOSTIMULANT MEDICATIONS**

Psychostimulants are prescription medicines that are approved in some countries for the treatment of attention deficit disorder (ADHD), narcolepsy, binge-eating, or obesity. They include medications from amphetamine class and methylphenidate. Modafinil is a psychostimulant medication not related to amphetamines but it increases the level of dopamine and noradrenaline in the brain in a manner similar to other psychostimulants (Madras *et al.*, 2006).

Multiple controlled studies evaluated the effect of prescription psychostimulants as a treatment of patients with methamphetamine and cocaine use disorder. Slowly accumulating evidence suggests that these medications may offer benefits in the treatment of PSUD and that the risks and benefits ratio for these medications is acceptable. Below, we briefly summarize the evidence from randomized treatment studies comparing effects of studied medications to a placebo control.

### ***Methylphenidate (MPH)***

Methylphenidate and its more potent dextrorotatory form dexmethylphenidate have demonstrated efficacy and are approved in many countries for the treatment of ADHD and narcolepsy. Methylphenidate is also used clinically in treatment of cancer-related fatigue.

Patients with moderate-severe amphetamine or methamphetamine dependence treated with MPH had longer retention in treatment, lower craving, less drug use, and lower risk of relapse than patients treated with placebo (Konstenius *et al.*, 2014, Ling *et al.*, 2014, Miles *et al.*, 2013, Rezaei *et al.*, 2015, Tiihonen *et al.*, 2007). All of those studies used an extended-release form of MPH in doses of 54-180 mg/d for a period of 10 to 24 weeks.

MPH was also tested as treatment for cocaine dependence. In one study, patients treated with MPH used less cocaine (Levin *et al.*, 2007) however there was no effect of MPH on cocaine use in two other studies (Grabowski *et al.*, 1997, Schubiner *et al.*, 2002). There was no effect of MPH on cocaine use in patients with opioid dependence treated with an opioid agonist, either methadone (Levin *et al.*, 2006) or medically prescribed diacetylmorphine (heroin) (Dursteler-MacFarland *et al.*, 2013).

In summary, methylphenidate might offer benefits in the treatment for amphetamine use disorder with less support for treatment of cocaine use disorder.

### **Amphetamines**

Several amphetamine products are registered as prescription psychostimulants. It includes medications containing amphetamine base or amphetamine salts (e.g., sulfate), either as a single enantiomer (dextroamphetamine) or a racemic mixture (dextro and levo amphetamine). Most frequently used amphetamine product is mixed amphetamine salts. A recently introduced amphetamine medication with a lower potential for misuse is lisdexamphetamine which is a dextroamphetamine prodrug. Methamphetamine also belongs to this class of medications.

Dextroamphetamine (and mixed amphetamine salts) is approved for treatment of ADHD and narcolepsy and is also used in treatment of depression. Methamphetamine is approved for treatment of ADHD and a short-term treatment of obesity not responding to other treatments. Methamphetamine is used infrequently because of the rapid development of tolerance to its appetite suppressant effects and high potential for non-medical use.

Patients with cocaine dependence treated with (extended release) dextroamphetamine (60 mg/d) or the mixed amphetamine salts (60-80 mg/d) had longer retention in treatment (Grabowski *et al.*, 2001) and higher rates of continuous abstinence (Levin *et al.*, 2015) with higher doses of the medication producing greater benefits.

Patients treated with extended release methamphetamine (30 mg/d) had lower craving and cocaine use (Mooney *et al.*, 2009). Patients treated with lisdexamphetamine 70 mg/d had lower cocaine craving but there was no effect on use (Mooney *et al.*, 2015), though the dose used in this study was relatively low (equivalent to 30 mg/d of dextroamphetamine).

Patients with cocaine dependence, who were also enrolled in maintenance program with a medically prescribed diacetylmorphine (heroin) to address their opioid dependence, had less

cocaine use and higher rates of continuous abstinence from cocaine while treated with extended release d-amphetamine dispensed daily in the clinic (Nuijten *et al.*, 2016).

Patients with methamphetamine dependence treated with dextroamphetamine (60 or 110 mg/d) had longer retention in treatment, lower craving, less withdrawal symptoms but there was no clear effect on methamphetamine use (Galloway *et al.*, 2011, Longo *et al.*, 2010).

In summary, amphetamine products, especially extended release preparations prescribed in higher doses, seem to offer benefits in the treatment for cocaine use disorder with less support for treatment of amphetamine use disorder.

### **Modafinil (MOD)**

Modafinil and armodafinil are psychostimulant medication approved for treatment of excessive sleepiness in patients with narcolepsy, sleep apnea, or shift work disorder. It is also used in treatment of ADHD, fatigue related to other medical disorders, and depression. As there is an elevated risk for misuse of modafinil, it is classified as a controlled substance, though with less restrictions than MPH and amphetamines.

Patients with cocaine dependence treated with MOD used less cocaine and had higher rates of continuous abstinence in several studies (Anderson *et al.*, 2009, Dackis *et al.*, 2005, Kampman *et al.*, 2015, Morgan *et al.*, 2016). However other studies did not detect the effect of modafinil on cocaine use or abstinence (Dackis *et al.*, 2012, Schmitz *et al.*, 2014, Schmitz *et al.*, 2012). Modafinil had no effect overall on the retention in treatment.

Patients with methamphetamine dependence treated with modafinil had no clear improvement in methamphetamine use or abstinence, however, modafinil might have some beneficial effects in selected group of patients who were adherent with the medication (Anderson *et al.*, 2012, Heinzerling *et al.*, 2010, Shearer *et al.*, 2009).

In summary, the usefulness of modafinil in treatment of amphetamine or cocaine use disorder is equivocal, and the overall benefits may be limited to selected group of patients which makes these findings less generalizable. It is possible however that a supervised treatment with modafinil might offer added benefits.

### **Psychostimulant medications: Safety Concerns**

Because MPH, amphetamine-based medications, and to some extent modafinil, can be used for non-medical purposes, they are classified as controlled substances, which imposes restrictions on their clinical use. Parallel regulatory restrictions are placed on opioid medications methadone or buprenorphine which are used for treatment of opioid use disorder. Prescription stimulants are generally well tolerated, even if taken on chronic basis, provided that their safety is closely monitored. For example, MPH or amphetamines should not be used in patients with a severe hypertension or a heart disease such as angina, arrhythmias, or heart failure (Levin *et al.*, 2018).

Psychostimulants are widely prescribed for the treatment of ADHD, often in children or adolescents, where these are given chronically with a very good long-term safety record (Fredriksen *et al.*, 2013). Nevertheless, these medications pose a risk for misuse and diversions, especially in adolescents and young adults and in individuals with substance use disorders. To ensure that the benefits of prescription stimulants outweigh their risks medical professionals can implement specific risk evaluation and reduction strategies. Two main strategies are utilized that support safe use of these medications: close monitoring and the use of preparations with lower abuse potential.

Both MPH and prescription amphetamines are available as immediate-release or extended-release preparations. Extended-release preparations are particularly suitable as a treatment for PSUD as these preparations provide a relatively stable blood level of the medication throughout the day with a single morning dose. By minimizing rapid increase or decrease of medication blood level, extended-release preparations are less likely to produce subjective effects (intoxication or withdrawal) thereby minimizing the potential for misuse of the medication.

Close monitoring of treatment may also diminish adverse effects of these medications. A single daily dosing makes these medications suitable for dispensing and administration under supervision, similarly to the manner that opioid agonists are often administered. This allows the medical personnel to educate and evaluate the patient before each dose and withhold the medication in case of safety concerns. If the patient needs to take medication at home, a limited number of doses can be given, which minimizes the possibility of medication diversion.



In prescribing any of the psychostimulant medications, a physician should weigh the risk of adverse outcomes against the potential therapeutic benefits. This evaluation should continue as long as the medication is used, where physician must decide whether the use or continuation of pharmacotherapy with stimulants continues to be beneficial or not.

## ANTIDEPRESSANTS AND OTHER PROMISING MEDICATIONS

### ***Bupropion***

Bupropion is a medication approved in many countries for the treatment of depression and as an aid to smoking cessation. Even though its chemical structure is similar to amphetamines, and it also increases the level of dopamine and noradrenaline in the nerve cells, the risk and incidents of bupropion abuse are very rare and therefore it is not classified as a controlled substance. Bupropion has been tested as treatment for stimulant use disorder because it is effective in treatment of depression and as an aid in smoking cessation. Moreover, its dopaminergic effects can make it useful in relieving stimulant withdrawal.

In patients with methamphetamine use disorder bupropion was only effective in patients that had low level of use, helping them to have longer periods of abstinence (Elkashef *et al.*, 2008, Shoptaw *et al.*, 2008b). However, replication studies did not confirm the benefits of bupropion (Anderson *et al.*, 2015, Heinzerling *et al.*, 2014). Bupropion had no effect on treatment retention or methamphetamine craving.

In patients with cocaine dependence, there was no beneficial effect of bupropion (Shoptaw *et al.*, 2008a), including in patients with co-occurring cocaine and opioid use disorder (treated with methadone) (Margolin *et al.*, 1995, Poling *et al.*, 2006).

In summary, bupropion has limited benefits in treatment of stimulant use disorder except in a subpopulation of patients with a mild methamphetamine use disorder.

### **Mirtazapine**

Mirtazapine is an antidepressant with a broad spectrum of pharmacological effects. Mirtazapine decreased methamphetamine use in patient with amphetamine dependence (Colfax *et al.*, 2011), however it had no effect on cocaine use in patients with cocaine use disorder (Afshar *et al.*, 2012). Due to the limited number of studies it is premature to recommend clinical use of mirtazapine.

### **Topiramate**

Topiramate is an anticonvulsant medication that has been used in treatment of alcohol dependence and was tested as a treatment for PSUD. Topiramate dose must be slowly increased over 4-8 weeks to avoid cognitive side-effects, therefore most studies evaluated the effect on drug use after several weeks of treatment.

Patients with cocaine dependence treated with topiramate had less cocaine use (Baldacara *et al.*, 2016, Johnson *et al.*, 2013, Kampman *et al.*, 2004). As indicated previously, a combination of topiramate and mixed amphetamine salts decreased cocaine use and increased rates of abstinence in patients with cocaine use disorder (Mariani *et al.*, 2012).

Higher level of abstinence from cocaine was shown in people with both cocaine and alcohol dependence treated with topiramate (Kampman *et al.*, 2013). However, topiramate had no effect in methadone-maintained patients with co-occurring opioid and cocaine use disorders (Pirnia *et al.*, 2018, Umbricht *et al.*, 2014).

In patients with methamphetamine use disorder, there was no effect of topiramate on the rates of abstinence (Elkashef *et al.*, 2012), however, patients treated with topiramate had less methamphetamine use over time (Ma *et al.*, 2013, Rezaei *et al.*, 2016) with the effect of medication most prominent in the people who were abstinent at the beginning of treatment.

In summary, the usefulness of topiramate in treatment of PSUD is equivocal. There is some indication that topiramate may be useful as a relapse-prevention strategy for individuals with a

period of initial abstinence at the beginning of treatment, such as patients treated at first in the residential treatment setting (Singh *et al.*, 2016). However, the dose of topiramate has to be gradually increased over many weeks to minimize cognitive side-effects.

### **Naltrexone**

Naltrexone is an opioid receptor antagonist approved for treatment of alcohol and opioid use disorder. In patients with cocaine use disorder who had an initial period of abstinence, naltrexone used in combination with relapse prevention CBT, but not alone, decreased cocaine use (Schmitz *et al.*, 2001). However, in another study naltrexone was only effective in patients who were non-abstinent at the beginning of treatment (Schmitz *et al.*, 2014). Naltrexone was not effective for patients with co-occurring cocaine and alcohol use disorders (Hersh *et al.*, 1998, Pettinati *et al.*, 2008, Schmitz *et al.*, 2009, Schmitz *et al.*, 2004)

Naltrexone reduced rates of relapse to amphetamine use and craving among individuals with amphetamine use disorder (Jayaram-Lindstrom *et al.*, 2008). However, replication studies using XR-naltrexone did not show benefits in patients with methamphetamine use who were abstinent at baseline and had overall low rates of detected relapse (Runarsdottir *et al.*, 2017). No reduction of drug use or craving was shown in patients with amphetamine use disorder who had high level of baseline use (Coffin *et al.*, 2018). Patients with amphetamine and heroin use disorder treated with XR-naltrexone (implant) had less use of amphetamine and heroin (Tiihonen *et al.*, 2012).

In summary, there is very limited support for the use of naltrexone in treatment of cocaine use disorder without co-occurring alcohol dependence and the evidence is equivocal in patients with amphetamine use disorder. Further studies may better characterize the sample of patients likely to benefit from naltrexone and the most effective strategy to use the medication.

### **Disulfiram**

Disulfiram is a medication used in the treatment of alcoholism. It blocks the enzyme breaking down alcohol which leads to the accumulation of acetaldehyde causing an unpleasant physical reaction following the ingestion of alcohol. Patients who are aware of this possibility are deterred from drinking alcohol which reinforces their desire to stop drinking. Several studies show beneficial effects of disulfiram on measures of cocaine abstinence and use in both patients with co-occurring alcohol and cocaine use disorders (Carroll *et al.*, 1998), in patients with cocaine use disorder without alcohol use (Carroll *et al.*, 2004), and in patients with cocaine use disorder treated for opioid use disorder with an opioid agonist (George *et al.*, 2000) though another study in patients maintained on methadone showed only transient benefits (Petrakis *et al.*, 2000). A more recent study in patients maintained on methadone showed the beneficial effect of disulfiram are seen in patients treated with the 250 mg/d while lower doses may actually increase cocaine use (Oliveto *et al.*, 2011). Disulfiram combined with naltrexone for the treatment of patients with cocaine and

alcohol use disorder increased rates of abstinence from both cocaine and alcohol (Pettinati *et al.*, 2008). Disulfiram has not been tested in clinical trials as a treatment of amphetamine use disorder.

In summary, there is some support for the use of disulfiram in patients with cocaine use disorder, with or without co-occurring alcohol use disorder. The dosing of disulfiram may need to be individualized, with average doses of 250 mg/d. Patients treated with disulfiram should be counselled and monitored about the potential of adverse reaction if alcohol is consumed.

### ***N-acetylcysteine (NAC)***

NAC is a medication that has favourable safety profile and is often available without the prescription. There is very limited evidence that NAC reduces craving in patients with methamphetamine use disorder (LaRowe *et al.*, 2007, Mousavi *et al.*, 2015) but not with cocaine use disorder (Schulte *et al.*, 2018). NAC is a promising medication (Duailibi *et al.*, 2017) but additional studies need to be conducted before it can be recommended for patients with stimulant use disorder.

## **PHARMACOLOGICAL TREATMENT OF STIMULANT USE DISORDER: CONCLUSION AND NEXT STEPS**

Currently available evidence lends support for the use of prescription psychostimulants as treatment of cocaine and amphetamine use disorder while the evidence supporting use of other medication is less clear. While high-quality controlled studies are limited in number, accumulating evidence shows a beneficial effect of methylphenidate or amphetamine products, and to less extent modafinil. The fact that all three medications with similar pharmacological effects were found to be beneficial, further supports this general pharmacological strategy.

The strongest evidence supports the use of extended release formulations of methylphenidate in the treatment for amphetamine use disorder and the use of extended release formulations of amphetamine products in the treatment for cocaine use disorder.

For all psychostimulant medications, higher doses were more effective than lower doses, and patients who were adherent with the medication had greater benefits. Administering medications under observation, using a model implemented in treatment of opioid dependence with methadone, could be considered to improve medication adherence, to reduced misuse and diversion, and assure greater safety of prescription psychostimulant treatment in patients with stimulant use disorder. At the same time, this approach may also be difficult to accept for some patients.

Available studies support the overall safety of this approach, with no major concerns about the safety or misuse of prescription stimulants in population of patients with stimulant use disorder. Sustained release preparations should be offered as the first line of treatment as these appear to have lower potential for misuse. There is, however, a potential for adverse cardiovascular events with methylphenidate and amphetamines, especially in patients treated with higher doses,

therefore an evaluation of cardiac risk factors and exclusion of higher risk patients is indicated (Levin *et al.*, 2018).

Out of the non-stimulant pharmacological interventions there is very limited evidence supporting benefits of topiramate, naltrexone and disulfiram while there is no sufficient support to recommend the use of bupropion, mirtazapine, or NAC.

Replication studies in variety of treatment settings, are needed to have greater confidence in the effectiveness and safety of pharmacological interventions. Studies conducted to date differed in the patient population and requirements for study inclusion (e.g., presence of other psychiatric or substance use disorders), the type and the dose of the medications, duration of treatment and the clinical outcome of interest. For example, most studies primarily looked at drug-use outcomes (e.g. abstinence) whereas other clinical endpoints may be equally important such as improvements in physical health, mental health, social functioning and patient-reported quality of life.

Moreover, the results of studies were not consistently positive, for example different beneficial effects were seen in different studies or with different doses of the medication used. Therefore, additional work is needed to more accurately determine the effective doses and types of the medication and the characteristics of patient that benefits from specific medication, using a “precision medicine” perspective.

However, considering the urgency of the problems in various parts of the world, we argue that selected prescription stimulant medications may be offered to selected group of patients with severe forms of the disorder for a clinical use under a “compassionate use” clause, as long it is medically safe. In such cases, doctors should inform their patients that the proposed treatment with the medication for their PSUD is not approved by the regulatory agencies, discuss the benefits and potential harms using a “shared decision making” perspective and document and monitor the outcomes and safety. Waiting many more years for additional research and confirmatory studies may not be an option in some communities that urgently seek solutions.

## **FUTURE TREATMENTS**

There are numerous pharmacological and other experimental treatments for stimulant abuse that are being tested in animals and to a lesser extent in humans (Davidson, 2016). Some of the more promising approaches are highlighted below.

Transcranial magnetic stimulation (TMS) is a non-invasive method for delivering an electric field pulses into the brain. Delivering many TMS pulses in sequences can cause long-term changes in neuronal excitability and specific behaviours (Diana *et al.*, 2017). Preliminary studies using TMS suggests a reduction in cocaine craving, choice, and intake (Bolloni *et al.*, 2018), and reduction in craving for methamphetamine (Su *et al.*, 2017). Treatment using TMS has generally very limited side-effects. If proved effective, TMS may have therapeutic value in countries where the use of medications which are controlled substances may be restricted.



Vaccines for cocaine and other drugs of abuse have shown promise in rodent models but have thus far not been so effective in human trials due to sub-optimal immune response generated by currently available vaccines (Heekin *et al.*, 2017).

The disruption of memory reconsolidation may be an effective approach to treat PSUD as weakening cocaine associated memories, using pharmacological or psychological interventions, may lead to decrease in drug use (Sorg, 2012). Finally, genetic approaches could be used to treat addiction and the many polymorphisms associated with addiction open up multiple targets for treatments (Brimijoin *et al.*, 2018). Further investments in novel approaches to treat PSUD are likely to offer therapeutic tools that could replace or be used in combination with currently available approaches.

### **MANAGEMENT OF SUBSTANCE-INDUCED MOOD, PSYCHOTIC, AND ANXIETY DISORDERS**

Co-occurring psychiatric disorders are common in patients with methamphetamine and cocaine use disorders, with rates as high as 50-65% (Torrens *et al.*, 2011). Differentiating psychiatric disorders that preceded the development of stimulant use disorder from psychiatric syndrome secondary to stimulant use may be difficult. Ideally, psychiatric syndromes that persist during extended abstinence from the stimulant would be considered as primary or independent of substance use. However, in practice this differentiation is often not possible, because the patient may not have long enough abstinence (Nunes and Levin, 2004).

Therefore, psychiatric symptoms that persist during the period of reduced stimulant use or complete abstinence should be treated. If it is not possible to have sufficient abstinence, the symptoms should also be treated. Untreated psychiatric disorder will decrease the chance that patient may have a good outcome of stimulant use disorder treatment. Primary psychotic or mood disorders (major depression or bipolar disorder) that precede the onset of stimulant use disorder should be treated according to the standard guidelines (Lingford-Hughes *et al.*, 2012).

Patients dependent on stimulants as well as other substances should be treated simultaneously for both disorders with available pharmacotherapies. If a combined treatment is difficult to implement, a more severe disorder, with greater health impact, should be targeted first. Opioid use disorder can be treated with methadone, buprenorphine, or naltrexone. Alcohol use disorder can be treated with naltrexone, acamprosate, or disulfiram. Naltrexone may reduce both stimulant as well as alcohol use. Disulfiram was also found to decrease both alcohol and cocaine use in some but not all trials. Combination of disulfiram and naltrexone have been found effective in patients who have combined cocaine and alcohol dependence (Pettinati *et al.*, 2008).

## CONCLUSION AND CALL FOR ACTION

Stimulant drug use is a widespread problem present in many countries. It imposes an enormous societal cost including economic, health, and social order costs and has a negative impact on the well-being of individual citizens and communities. The majority of stimulants are consumed by a small number of individuals who have a stimulant use disorder (PSUD). In those individuals drug use can be reduced or eliminated by addressing its determinants and consequences using health-based solutions – primarily treatment but also policies and programs in the areas of prevention and early intervention, community-based outreach, and recovery management.

At present, treatment for PSUD is available to less than 10% of people with PSUD who need treatment. Moreover, individuals that receive treatment most often do not receive evidence-based treatment, rather they receive less effective, ineffective, or even harmful interventions. Very often, individuals who use stimulants are not interested in treatment offered to them because they do not believe it will be useful, they find treatment too demanding, and may find treatment that it does not offer medications or other medical interventions as unappealing.

Therefore, it is imperative to promote effective, evidence-based treatment to narrow the gap between science and practice and to promote practices that respect human rights and suppress those that do not. This imperative has been widely recognized and accepted by the international agencies such as CND and most professional organizations. The goal of the UNODC and WHO joint Program on Drug Dependence Treatment and Care Program is to promote and support evidence-based and ethical policies, strategies, and interventions to reduce the health and social burden of stimulant drug use.

The present document summarizes the latest scientific evidence on effective interventions to treat PSUD. Several pharmacological interventions as well as a set of specific psychosocial interventions have been shown to reduce use of stimulants in individuals with PSUD which is likely to result in improvement in health and a positive impact on the communities. In the opinion of experts, there is sufficient evidence from research studies to support the development of treatment protocols that could be used in the community-based practice

The next stage of the effort to close health services gap is to develop specific evidence-based treatment protocols and to conduct an implementation trial treatment using these protocols for individuals with PSUD in several countries. To accomplish that the convened UNODC Expert Group propose to establish a network of addiction treatment sites, a Stimulant Use Disorder Treatment Research Collaborative. Treatment programs located in various countries and communities will become sites for projects that aim to implement and evaluate the outcome of the shared treatment protocol for patients with PSUD.

The proposed research collaborative will consist of the Coordinating Node and a network of sites that are available to implement research trial as a part of the Collaborative. The coordinating

node will be responsible for administrative and financial coordination, research planning and oversight, data management and quality control, training and education, and a technical support to all sites. Each of the sites will have an identified person responsible for the execution of research protocols and an administrator.

As the first project for the research collaborative we propose to evaluate the implementation of the outpatient protocol for treatment of individuals with severe PSUD. We propose to enrol sites that will treat patients with amphetamine use disorder and sites that will treat patients with cocaine use disorder. Treatment protocol will include a supervised administration of a prescription psychostimulant medication given in combination with a psychosocial intervention. We



We propose a trial of an extended-release preparation of mixed-amphetamine salts for patients with cocaine use disorder and extended-release methylphenidate for patients with amphetamine use disorder. The psychosocial intervention will follow a manualized program that include elements of MET/MI, CBT, CM, and psychoeducation. We propose a 6 month-long trial with the primary outcome of a sustained abstinence from illicit stimulants.

The primary objective of the proposed program of research is to conduct a large implementation trial to demonstrate the effectiveness of the new treatment protocol in a variety of patient populations, treatment settings, and countries. We propose to carry out the project in three stages; 1) Development phase, 2) Pilot trial phase, and 2) Multisite replication and a hypothesis-testing study.

Additional goals of the project include the development of implementation packages to engage professional staff at test sites and to make it possible for them to overcome barriers and to start using the evidence-based treatment protocol in daily practice. Subsequently, the project aims to help built systems to support and institutionalize the use of the evidence-based treatment of PSUD in a variety of countries and in a sustainable way to maintain daily use of practices that adhere to the principles and procedures outlined in guidelines proposed in this document.

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