Drug Abuse: Addiction and Recovery

Chapter 2

Licit Drug Withdrawal: Symptoms and Treatments

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Abstract

Abstinence is the deprivation of previously abused substances that lead to addiction. The long-term and excessive use of a drug causes different biochemical and neurophysiological changes. After addiction is established, deprivation causes withdrawal, whose symptoms, duration and degree vary among substances. Common symptoms include anxiety, depression, tremors, impaired thinking, and changes in autonomic nervous system functioning (tachycardia, sweating, vomiting). The most widely used licit drugs of abuse are alcohol and nicotine, and although both are considered psychoactive substances, abstinence from each differs in both neurophysiological and behavioral terms. When substance use is deemed abusive and intervention is necessary, treatment includes medical care and medication to decrease symptoms, avoid complications, and prevent patient craving. A number of prescription drugs are available for the treatment of addiction and withdrawal from alcohol and nicotine. Although treatment for more severe cases may help significantly, most individuals abandon treatment and relapse. Thus, new approaches and experimental tests have been developed in order to expand knowledge about the systemic effects of abusive drugs and alternatives to rehabilitation treatments. In this respect, this chapter intends to review the state of the art in the study of addiction and abstinence from alcohol and nicotine, and propose alternatives for addiction and abstinence treatment.

1. Introduction

Throughout human history, mankind has used drugs for pleasure or healing purposes [1]. Many of these drugs are potentially addictive, characterized by the continuous use of a substance despite its harmful consequences [2]. Drug addiction is considered a worldwide epidemic related to genetic, physiological and environmental factors that lead to health and socioeconomic problems [3]. In the United States, it is estimated that around 21.5 million adults suffer from substance abuse disorder, alcohol being the main addictive substance consumed [4].

Once addiction is established, substance withdrawal can be an arduous and painful challenge. Heavy and long-term drug consumption causes persistent changes in the neural circuitry and behavior [5]. After a period of drug discontinuation, the nervous system has to readjust to the absence of the substance, giving rise to a set of different symptoms, characterizing the withdrawal syndrome [6]. The onset of symptoms varies among drugs, generally occurring within a few hours and peaking in a few days [7,8]. It usually involves somatic, affective and cognitive manifestations [9]. Some symptoms of this syndrome are opposite to those that occur under drug action, a phenomenon known as the "opponent process" [10,11]. Withdrawal from depressants such as alcohol is accompanied by increased anxiety and agitation [5,6]; by contrast, common symptoms of withdrawal from stimulants such as nicotine are fatigue, psychomotor impairment and depressed mood [12,13].

Some addictive drugs are prohibited worldwide, while others are regulated according to the country or state. There are also substances that can be medically prescribed, such as cannabis [14]. On the other hand, oft-addictive and licit drugs such as alcohol and tobacco, which are easily acquired, are only restricted by age. Approximately 2.5 million deaths per year are attributed to alcohol, while cigarette smoking accounts for another 5.4 million deaths (WHO, 2010; 2011). The consumption of these drugs and the associated problems vary widely and remain significant in most countries. Alcohol and nicotine together are a causal factor and/or component cause in several diseases, greater than HIV and tuberculosis combined (WHO 2010; 2011).

Nicotine is a brain stimulant and the major psychoactive component of tobacco. The consumption of this substance produces positive reinforcement, and users report increased energy, attention and relaxation when using nicotine under stress [15]. However, regular use of tobacco can cause cancer, respiratory diseases, neurodegenerative diseases and death [16-18]. According to the World Health Organization (WHO 2015), tobacco has caused 100 million deaths in the last century. Nicotine consumption can start early in life: reports show that the first experience with cigarettes occurs around the age of 13-14 years [1] and is correlated with late consumption of other drugs such as cocaine and marijuana [19]. Adolescents are substitut-

ing common cigarettes with flavored cigars [20]; electronic cigarettes are also very common and claim to be healthier, despite the fact that they contain the addictive substance [19]. In the Diagnostic and Statistical Manual of Mental Disorder (DMS-5), quitting or reducing cigarette consumption leads to tobacco withdrawal syndrome, which is characterized by increased anxiety, difficulty concentrating, depressed mood, increased appetite, insomnia, irritability, and restlessness.

Alcohol depresses the central nervous system, initially producing an anxiolytic effect [21,22]. Repeated consumption leads to tolerance and higher amounts of alcohol are necessary to achieve the same effects [23,24]. This substance is associated with a number of diseases, including alcohol dependence, cirrhosis, cancer and fetal alcohol syndrome, in addition to an increased risk of infectious diseases, car accidents and violent behavior. It is estimated that 5.9% of deaths worldwide occur due to alcohol consumption (WHO 2014). When a person becomes an alcoholic, symptoms of alcohol withdrawal syndrome appear after just a few hours of deprivation. The syndrome is characterized by autonomic hyperactivity, tremors, anxiety and restlessness. In more severe cases it can be accompanied by seizures, hallucinations and delirium, the last emerging after 3 days of withdrawal and lasting for 48 to 72 hours [25].

Despite substance abuse and addiction's being a serious health problem, withdrawal symptoms hinder drug cessation, increasing the chance of relapse. Although with different degrees of severity, the licit drugs discussed here have the potential to cause intoxication, chronic health problems and death. In this respect, effective treatments are essential. However, treatments could also be a challenge, since they require not only medical/pharmacological intervention, but an integrative approach that relieves craving and withdrawal symptoms, thereby changing an individual's perspective on life and the future. As such, understanding the mechanisms underlying addiction and withdrawal may be key to developing targeted interventions that will overcome the obstacles in current treatments and avoid relapse [26].

2. Neurochemistry Bases

Different addictive drugs act on different neurotransmitter systems in the brain, but all stimulate the dopaminergic system, increasing dopamine levels [27,28]. This neurotransmitter plays an important role in reward processing and reinforcing behavior. The addictive drugs increase up to 10 times the levels of dopamine in the brain and change the normal dopamine secretion leading to the need for more dopamine that only the drug can cause. In mammals, areas of the brain such as the ventral tegmental area (VTA), the nucleus accumbens (NAc), prefrontal cortex (PFC), the amygdala and the hippocampus seem to be related to addictive behavior [29]. Thus, the long-lasting behavioral consequences of the drugs are related to persistent changes in the brain, which only disappear long after the drug removal [30,31]. After neuroadaptation has been established, drug cessation may trigger a negative state (somatic and

affective) that contributes to drug dependence through negative reinforcement [32]. All the oft-addictive drugs function in this manner, including the most available and licit ones: alcohol and nicotine.

2.1. Alcohol

Alcohol or ethanol is a central nervous system depressant that acts through different mechanisms. For instance, alcohol mainly affects the transmission and function of the glutamatergic and GABAergic systems, as well as the adenosinergic and cholinergic systems [33]. It exerts a biphasic effect on brain activity, characterized by initial short-term stimulation, followed by depression in brain activity [34]. The acute alcohol effect is mediated by agonistic and antagonistic action on gamma-aminobutyric acid type-A (GABAA) and N-methyl-D-aspartate (NMDA) receptors, respectively [35,36]. However, prolonged alcohol consumption causes overstimulation of GABAA receptors, which culminates in its down-regulation, while on the other hand, NMDA receptors are up-regulated in order to maintain glutamate response [37]. Thus, the individual can develop tolerance to alcohol and higher amounts of the drug are needed to achieve the initial effects [38]. During alcohol withdrawal, absence of the drug causes hyper excitation of the nervous system, and the neuroadaptations derived from chronic intake initiate the reversal process [39,40].

Two major symptoms of alcohol withdrawal, namely seizures and delirium tremens, are consequences of substance interaction with NMDA receptors. Long term alcohol use increases the expression of NMDA receptors (NR1 and NR2B), due to the inhibitory effects of the drug on these receptors functioning. When the receptors density is increased and alcohol intake is absent, the normal glutamate secretion over stimulates the system, characterizing the hyper excitation state observed during withdrawal [41,42]. Studies have shown that NMDA plays a key role in the appearance of seizures [41,43,44]. For instance, blockade of NMDA receptors in hippocampal neurons eliminates this symptom [41]. In addition to direct NMDA activity regulation, continued alcohol exposure heightens voltage-dependent calcium channel activity [45], which may increase gene expression related to NMDA and GABA receptor synthesis [40,46]. Taken together, alterations in calcium influx caused by the effects of alcohol on voltage-dependent and ligand-dependent channels, such as NMDA, contribute to the emergence of withdrawal symptoms [46].

Activation of NMDA receptors enhances the expression of the early immediate gene c-fos, related to long-lasting central nervous system changes. Indeed, mRNA c-fos levels are high in different brain areas under alcohol abstinence [47]. Glutamatergic transmission is also exacerbated by the excitatory action of homocysteine, an amino acid whose levels increase due to alcohol intake [48]. Higher levels of homocysteine are predictive of withdrawal seizures, which might occur due to exacerbation of glutamatergic neurotransmission [48].

Seizure occurrence also seems to be modulated by GABA, since the administration of bicculline, a GABAA antagonist, reduces seizure thresholds [49]. Chronic alcohol use decreases the expression of GABAA receptors, due to the stimulatory effects of the drug on these receptors functioning that culminate in down regulation. The decreased GABAA receptor density is observed in combination with the increased expression of other subunits that are less sensitive to alcohol [50]. Thus, in the absence of the drug, the amount of GABA neurotransmitter normally secreted becomes insufficient to affect the post synaptic neurons that express decreased number of receptors. In the amygdala, a change in GABAA receptor activity is associated with anxiety [51]. In rats under alcohol abstinence, treatment with GABAA and GABAB receptor agonists attenuated anxiety, a result not observed in animals treated with glutamate receptor agonists [52].

Monoamines and catecholamines are also involved in the alcohol withdrawal syndrome. Dopamine receptor binding increases in key emotional processing regions during withdrawal [53]. Withdrawal also raises plasma adrenaline and noradrenaline levels, with the ratio of noradrenaline to adrenaline correlated with the severity of hyper excitability promoted by withdrawal [54]. In humans, plasma noradrenaline levels are higher after drug cessation, but serotonin levels decrease [55]. Evidence suggests that serotonin and noradrenaline are also related to alcohol abuse in animal models [56-58], and seem to mediate craving and relapse during withdrawal. However, this relation is not clear and further studies are needed for a thorough understanding [55].

Alcohol withdrawal syndrome is a complex disorder regulated by different neural mechanisms. Initially, after alcohol abuse for a long time, the drug cessation creates a general excitatory activity due to GABA and NMDA system neuroadaptations that lead to increased anxiety, seizures and delirium tremens. Some mechanisms remain unclear and the molecular basis of tolerance and craving is poorly understood.

2.2. Nicotine

Nicotine is a psychostimulant drug associated with cognitive improvement [59] and acts as an agonist on different subtypes of nicotinic acetylcholine receptors (nAChRs) [60]. These receptors play an important role in neuronal functions, including excitability, cognitive function and plasticity induction [61,62]. Nicotinic receptors are ligand-gated ion channels with high permeability to Ca^{2+} [62]. The subunits are classified into two families: the α-type (α2-α9) and β-type (β2, β3 and β4), but most receptors are formed by the coexpression of α and β subunits [63], one of the most common being the α4β2 receptor [64].

Nicotine is a full agonist of α4β2 and α7 nAChRs, but shows higher affinity for the former [59]. The binding of nicotine at acetylcholine receptors can also increase the release of dopamine, the neurotransmitter that exerts positive reinforcing effects and may lead to the

drug dependence [65]. The neuroadaptations resultant of long-term drug consumption and addiction are responsible for the physiological and behavioral symptoms during withdrawal.

Neuroadaptation related to long-term drug consumption and addiction is responsible for the physiological and behavioral symptoms during withdrawal. In the case of nicotine, a relevant withdrawal symptom is the decrease in cognitive performance that manifests itself for several days after cessation [66,67]. Nicotine activates nAChRs in the hippocampus, an important area for attention, learning and memory, in addition to inducing synaptic potentiation [68]. Chronic consumption leads to long-lasting changes in this region, which is affected by drug withdrawal. Studies have shown that α4β2 and α7 nAChRs can act differently in withdrawal-induced deficits. In mice, administration of the α4β2 agonist (i.e. varenicline) reduces withdrawal deficits in fear conditioning; however, the α7 agonist cannot reverse the animal's poor performance [69]. On the other hand, impaired attention due to withdrawal is related to the α7 receptor, since mice lacking this receptor show no withdrawal-induced deficits [70].

Another system involved in nicotine effects is the endocannabinoid system [71,72]. 2-arachidonoylglycerol (2-AG) is an endogenous endocannabinnoid that attenuates the somatic signs of nicotine withdrawal [73]. 2-AG concentration was shown to increase 10 minutes after withdrawal [74]. Despite the positive effect on physical withdrawal symptoms, activation of CB1 receptors by 2-AG is associated with cognitive impairment. Mice submitted to pharmacological or genetic inactivation of CB1 receptors in forebrain GABAergic neurons exhibit no memory deficits during nicotine withdrawal [74]. In addition, these authors found that nicotine withdrawal reduces the density of mushroom-type dendritic spines in the hippocampus, which was reversed in mice lacking CB1 receptors in GABAergic neurons. In the hippocampus, dendritic spines are important to the structural changes in synapses that underlie the learning and memory process [75]. Moreover, mushroom spines contain a high density of glutamate receptors [76,77].

The glutamatergic system has been related to many aspects of nicotine withdrawal. Nicotine induces glutamate release and activates presynaptic glutamate terminals, causing a stimulatory effect on dopamine transmission and activation of postsynaptic metabotropic Glu5 receptors, which are implicated in the reinforcing properties of nicotine [78,79]. With respect to withdrawal, these receptors participate in the somatic and affective manifestations of abstinence. Mice with metabotropic Glu5 receptor knockout showed attenuation of anhedonia and somatic withdrawal signs [78].

Many neurotransmission systems and mechanisms are involved in nicotine addiction and withdrawal. This substance can change the long-term structure and activity of the neural system. As such, its absence disrupts the newly acquired homeostasis related to the drug. Cognitive deficits and depressed mood due to withdrawal are the main causes of relapse. While

treatments are available, not all are efficient, and most patients relapse. In this respect, more studies are needed to fully understand the neural mechanisms of nicotine withdrawal.

3. Models in Addiction and Withdrawal Research

Understanding the neurobiology involved in drug withdrawal requires novel approaches to properly model the withdrawal syndrome. This can be achieved through new experimental paradigms, new biomarkers and alternative research models [80].

Drug withdrawal symptoms can be recognized and self-reported by those who experience them, and are expressed as changes in mood or behavior. The symptoms of nicotine withdrawal start about 30 min after the last use, and depend on how much has been used and for how long. Symptoms include cravings, tingling, sweating, nausea, headaches, insomnia, attention and learning deficits, anxiety, irritability and depression. Alcohol withdrawal symptoms start from 6 to 12 h after the last intake, and be more severe between 12 and 24h after ingestion, depending on how much was consumed and for how long. They include tremors, sweating, hypertension, tachycardia, and general delirious symptoms such as clouded consciousness, disorientation, disturbed circadian rhythms, thought processes and sensory disturbances, all of which fluctuate over time [81].

Clinical studies on abstinence in humans are usually retrospective, that is, first a volunteer exhibits withdrawal symptoms and is then investigated or the possible generating events of the process are recreated. Scientific control becomes more difficult when it involves human testimony, since it depends entirely on the veracity of the doses and percentages reported by each person. However, many of the withdrawal symptoms observed in humans are also observed in animal models, with the advantage of researchers controlling the exposure regime and amount. Thus, scientists are using animals as subjects to model the symptoms of drug withdrawal. Since withdrawal from these drugs of abuse commonly produces symptoms of anxiety, animal models of anxiety could be useful for studying drug withdrawal.

Alcohol withdrawal signs have been described in rats [82-85], mice [86-88], cats [89,90], dogs [91,92], fish [24,93] , monkeys [94] and chimpanzees [95,96]. These species and humans exhibit tremors and potentially fatal seizures during alcohol withdrawal.

In line with clinical findings, data on rodents describe anxiety-like behaviors evoked by acute withdrawal from alcohol [97] and nicotine [98]. In addition to the robust behavioral effects of a single withdrawal period, repeated administration and cessation of a drug treatment in animal models evoke strong withdrawal-like effects. For instance, increased anxiety-like behavior was reported in rodents following repeated withdrawal from alcohol [99].

Numerous studies on the effects of nicotine abstinence in animal models induce ab-

stinence using an 'extinction' procedure, in which the experimenter either stops delivering nicotine or no longer rewards animal responses with nicotine [100]. Both of these procedures exhibit problems. Most animal studies involve experimenter-administered nicotine. In many models, an experimenter-administered drug produces dramatically different neurobiological outcomes than a self-administered one [101]. Thus, cessation of an experimenter-administered vs. self-administered drug likely produces different results. Whether this is true for alcohol and nicotine deprivation has yet to be tested. However, there is a consensus that interrupting self-administered drugs appears to be more generalizable and translational than halting experimenter-administered drugs.

The withdrawal syndrome is one of the indicators of a drug-dependent state, which is often paralleled by drug tolerance, due to adaptations that take place within the body and the brain. In animal models, drug administration and drug withdrawal tests to determine the additive effect are more difficult, since there are only a few drug self-administration models. However, there are a number of behavioral tests to evaluate this condition. Two approaches for developing these models are presented here: Conditioned Place Preference (CPP) and Voluntary Intake.

The conditioned place preference is a common alternative to drug self-administration. In the CPP protocol, the motivational properties of the drug serve as conditional stimulus that is repeatedly paired with a series of environmental cues. During conditioning, these cues acquire secondary motivational properties [102-106]. The CPP protocol is useful because addiction is a psychiatric disorder that leads to compulsive drug-seeking behavior. As such, an animal that is conditioned to receiving a drug in a specific place will continue to seek it out long after the drug is removed [107]. The drug-induced conditioned place preference protocol offers a number of benefits, such as being a noninvasive (animal does not need to be handled, injected, etc.) and simple procedure that can be applied to studies investigating the addictive potential of many drugs of abuse [108-111]. In the CPP procedure, the conditioning phase does not usually last long due to the addictive power of the substances used. Thus, a single exposure may be enough to trigger compulsive drug seeking. Craving behavior, characterized by loss of control, and also referred to as compulsive drug seeking, shows high correlation with an increase in dopaminergic transmission in the mesocorticolimbic system [112]. However, even though CPP has long been used in science, the genetic and neurological bases of seeking behavior are not fully understood. It would be important to use CPP as a tool to develop pharmacological and psychological therapies for drug addiction and withdrawal treatment.

An alternative approach to study drug addiction and withdrawal is the drug self-administration protocol. This non-operant method is typically used for the oral route of administration, but is also available for inhalation or injection by the animal itself. The protocol is largely applied in rodent research, since the animals can access the drug in bottles (dissolved in liquid)

or food and ingest the desired amount. Ingesting the desired amount of the drug confers face and construct validity onto the protocol because it matches human alcohol consumption. It can be useful in the development of pharmacological interventions that prevent excessive intake or even lead to complete avoidance. Moreover, following the development of addiction/dependence and the neural and behavioral changes linked to it, researchers can address inter-subject differences and the neurobiological mechanisms underlying addiction. For instance, many strains or rodents selected for high and low alcohol preference have already been produced, allowing more detailed research on the genetic and environmental background that drives addiction [113].

4. Treatments Available

Drug addiction treatments are commonly believed to involve an individual's being arrested, locked up, forced to withdraw from drugs for several months, and then released onto the street. However, this is not always the case. Treatments for drug addiction and withdrawal symptoms can take several forms and degrees of effectiveness. Some users require a long withdrawal period, and suffer numerous relapses before being successfully treated, others withdraw quickly after stopping drug use, while some do not respond to any form of treatment.

Treatment does not require total abstinence, but can be considered successful with a reduction in drug use, even if not completely eliminated. Long-term drug use provokes changes in the brain systems (discussed above), thereby hindering abstinence, both psychologically and physiologically. Indeed, addiction is a brain-based disorder driven by biological and environmental factors. Recent research on drug use/abuse has shown that addiction has many different origins, including inherited traits (genetically and epigenetically), environmental/social pressure, personal habits and other indeterminate causes. Thus, to treat addiction one must face a myriad of causes and a lifestyle change involving both medical (pharmacological) and behavioral (psychological) treatments.

It is important to underscore that there is no single, highly effective treatment that can be universally applied. Different treatments have to be used in sequence or simultaneously to achieve success, and sometimes it takes longer to discover the best treatment approach for drug addiction. As such, many patients abandon treatment during the initial trials. It is also important to be resilient and have strong support from family and friends, so that the user who does not achieve immediate success will attempt an alternative treatment. A good treatment must contend with multiple problems, including family history, life history (anxiety, depression), and social history. Since many different elements contribute to drug use/abuse, it is difficult to remain drug-free without perceiving the whole picture. Moreover, many drug users are at a point where their lives are in shambles and simply stopping drug use may lead to an even more severe state. Thus, treatments have to include new opportunities and users often

need to rebuild personal and social skills through psychological therapy. Rehabilitation is usually prolonged and must be continued even after the individual is drug free. Therapies should be combined with medication, which helps in the physiological control of the addiction/withdrawal. Moreover, for those displaying anxiety/depression, medication and therapy to treat these specific disorders should be applied in conjunction with the drug addiction treatment.

Many treatments commence with a decrease in drug intake (not absolute withdrawal), so that detoxification can occur gradually. The brain systems can better deal with drug removal by slightly reducing the amount, so that the brain enzymes, neurotransmitters, and receptors can up regulate to function adequately without the drug. This avoids withdrawal syndrome and the most painful and difficult phases may be less arduous. However, it is not easy to determine how much to use or not use to avoid entering withdrawal while constantly reducing drug intake. As such, it is important to obtain the patient's personal and drug history in order to provide the most adequate treatment plan, which should involve behavior modification and medication to help the patient tolerate abstinence.

Behavior therapies use plans and practices to modify seeking behavior (craving), toxic behavior and drug intake. This can be done individually or in groups (for example: Alcoholics Anonymous), depending on the best plan for the patient. However, these therapies carry pros and cons. For instance, while individual therapies can meet specific needs and delve deeper into an individual's problems, group therapies may be cheaper, and more experienced members can serve as models to newcomers. Family therapy can also help if members are available to assist and support the patient.

Many types of behavior therapies are applied to treat addiction, such as cognitive behavioral therapy, which helps the intellectually-oriented patient avoid relapse [114], or contingency management, which uses reward to divert the patient from risky behavior [115]. Several others can be used, depending on the drug, level of addiction and other aspects of the patient's life. A recently proposed association between behavioral therapy and physical exercise showed a decline in seeking behavior in high school students [116]. However, further investigation is required to be used as a parallel instrument in the war against addiction.

With respect to medication, considerable research has been conducted on the mechanisms of action and benefits of the medications suggested to treat addiction. For alcohol addiction, the most common medications are naltrexone (an opiate receptor antagonist that inhibits alcohol seeking behavior; [117]) disufiram and clonidine (to induce nausea if alcohol is consumed; [118,119], ondansetron and topiramate (serotonin receptor antagonist and anticonvulsant, respectively, more recently applied with promising results; [120,121]). For nicotine addiction, gums and patches containing nicotine attempt replace the source of the drug and reduce smoking, but other drugs such as varenicline (nicotinic receptor agonist; [122]) and

bupropion (dopamine reuptake inhibitor [123]) are also used with relative success.

It is paradoxical to replace an addictive drug with medication or a different form of the same drug, as is the case of gums containing nicotine. While some argue that it does not help withdrawing from the drug, medications are part of a treatment that will help users free themselves from addiction and/or withdrawal, but additional steps are necessary to achieve complete rehabilitation. It is important to know that after prolonged drug intake and addiction, the user's brain systems are altered and the drug becomes part of its functioning. Thus, it is not easy to maintain proper brain function if the drug has been withdrawn. Slowly removing/replacing the drug may be useful in stabilizing the system while the user's behavior and physiology is being remodeled. For this reason, current knowledge recommends both behavior and medical therapies, but new research and insights are emerging and may lead to a different view of addiction treatment in the near future.

5. Alternative Treatments

Stress is a significant contributor to drug abuse and relapse [124-128]. It is known to increase drug use in general and alcohol and cigarettes in particular [129]. However, recent research suggests that mindfulness-based cognitive therapy, physical exercise and/or an alternative pharmacological intervention using ayahuasca are promising in drug addiction treatments.

Mindfulness reduces stress and has a potential impact on drug use and relapse. The technique is based on the user's awareness and acceptance of their experience and interruption of the craving/using/relapse cycle. It teaches how to process situations that may lead to relapse, inducing users to monitor their internal state, and react using mindful awareness, thereby making positive choices.

While cognitive-behavior treatment uses a reinterpretation of the situation with a more positive view and coping with stress [130,131], mindfulness treatment suggests accepting and viewing a negative situation as it is, then changing how one reacts to it [132]. Studies of meditation interventions as a treatment for alcohol users have shown positive results [133-135]. The use of mindfulness-based treatment has been garnering data that corroborate its successful effects on drug addiction [136,137], suggesting long-term benefits.

It is believed that reducing stress underlies the efficacy of mindfulness treatment in decreasing drug use and relapse over time [129]. Mindfulness treatment seems to be related to the control of stress outcomes in the amygdala and insula [129], areas also implicated in anxiety and anxiety disorders [138,139]. Neuroplasticity in these two structures was observed following mindfulness meditation (e.g., [140-144]). For instance, a decline in amygdala density is related to stress reduction [142] and mindfulness treatment decreases nicotine use [129].

Some authors have recently suggested the value of physical exercise as an alternative intervention to avoid drug relapse [145]. It is suggested that physical exercise exerts reinforcing effects, increasing some neurotransmitters levels that the addicted brain searches for, such as serotonin and dopamine. In fact, it was shown that exercise (wheel running) reduced ethanol seeking in rats [146], suggesting positive effects of voluntary physical exercising during withdrawal that may reduce relapse.

Other positive results associated with drug use are reported after ayahuasca-assisted treatment. Ayahuasca is a brew obtained by decoction of the bark and stems of *Banisteriopsis caapi* and leaves of *Psychotria viridis*, produced by indigenous groups in the Amazon for centuries [147]. The resulting brew, rich in N,N-dimethyltryptamine (DMT) and monoamine oxidase inhibitors (MAOIs), modulates the availability of monoaminergic neurotransmitters in the synaptic cleft. Ayahuasca consumption has been shown to activate brain areas related to emotions and memory [148], and users have reported improved concentration, better performance in cognitive tasks and a greater sense of meaning in their lives. As such, ayahuasca has recently gained attention as an alternative drug for treating mental disorders such as anxiety and depression, as well as drug addiction.

Ayahuasca intake is usually associated with positive lifestyle changes: people that experience the effects of ayahuasca have reported mind healing, increased self-knowledge, a sense of the meaning of life and persistent good mood states even after a single dose. Ayahuasca is often related to deep feelings and memories, and opportunities to re-evaluate negative behavior, events that lead to profound changes in an individual's life perspectives and expectations [149,150]. Thus, ayahuasca has been suggested as an alternative treatment for drug addiction due to its fast response, prolonged effect, absence of adverse effects and no addictive potential [151].

A number of studies have related ayahuasca consumption to reduced use of other abused substances [152-154]. The main action of ayahuasca in the brain occurs in the serotonergic system: DMT enhances the activation of 5-HT receptors (agonist effect), culminating in effects similar to those of serotonin itself. In regard to addiction, ayahuasca reduces dopamine levels in the mesocorticolimbic pathway through its action on 5-HT2A receptors expressed in dopaminergic neurons [155]. Participants in ayahuasca rituals significantly curb or even cease to take drugs of abuse, including cigarettes, alcohol and cocaine [153]. Studies in rodents showed that ayahuasca reverses alcohol sensitization [156], corroborating its potential to inhibit alcohol abuse.

6. Conclusion

Evidence of the aforementioned positive effects of mindfulness-based and ayahuasca treatments suggests therapeutic benefits. However, additional studies are needed to corrobo-

rate the positive effects of these two promising interventions. As stated above, alcohol and nicotine addiction are significant social and health problems. These two oft-addictive drugs are inexpensive and easily obtained, thereby increasing the likelihood of abuse. Consuming these drugs may lead to changes in the central nervous system that result in addiction, followed by withdrawal symptoms that impede drug cessation. While many treatments using alternative medication and therapies are available, relapse rates are between 40 and 60 percent. Thus, investment in new research and approaches to the addiction/withdrawal problem are needed. Recent techniques such as mindfulness, exercising and ayahuasca seem promising, but require more detailed investigation.

7. References

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