Serotonergic Hallucinogens and Emerging Targets for Addiction Pharmacotherapies

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KEYWORDS

• Serotonergic hallucinogens • Addiction • Treatment • Pharmacotherapy

KEY POINTS

- Converging lines of evidence from pharmacologic, electrophysiologic, and behavioral research in animals strongly suggest that activation of cortical 5-hydroxytryptamine-2A receptors is the most critical step in initiating a cascade of biological events that accounts for serotonergic hallucinogen (SH) psychoactive properties.
- Psilocybin produces hyperfrontality with divergent prefrontal–subcortical activation in such a way as to increase cognitive and affective processing in the context of reduced gating and reduced focus on external stimulus processing.
- In contrast to all other drugs of abuse, SHs are not considered to be capable of producing sufficient reinforcing effects to cause dependence (addiction) syndromes.
- Given that SHs increase extracellular glutamate levels and activity in the prefrontal–limbic circuitry, it is possible that a normalization in functional connectivity in this network through a glutamate-dependent neuroplastic adaptation could produce an anti-addictive effect.

INTRODUCTION

Hallucinogens are a broad group of drugs that are narrowly defined in the DSM-IV[1] to include only:

1. Serotonergic hallucinogens (SHs), agents that activate the 5-hydroxytryptamine-2A (5-HT_{2A}) receptor (2AR) such as lysergic acid diethylamide (LSD) and psilocybin

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2. The mixed amphetamine hallucinogen 3,4-methylenedioxymethamphetamine (MDMA [Ecstasy]).

However, they more broadly can include:

1. Dissociative anesthetics or *N*-methyl-D-aspartate (NMDA) antagonist hallucinogens (agents that antagonize the NMDA glutamate receptor such as phencyclidine [PCP], ketamine, and dextromethorphan)
2. Cannabinoid agonists (agents that activate the CB1 receptor)
3. κ opioid agonists (ie, salvinorum A)
4. Antimuscarinic agents (ie, scopolamine, atropine).

Most hallucinogens are included in the schedule I category as originally defined by the Controlled Substances Act of 1970.[2] As such, by definition they are classified as having no currently accepted medical use in the United States, lacking in safety for use under medical supervision, and possessing high addictive liability. From an addiction perspective, it is worth examining the evidence base for this classification to understand the true addictive liability of this class of agents. Moreover, given the history of research suggesting a role for certain hallucinogen treatment models to treat addictive disorders, it is further worth exploring how some of these drugs may confer anti-addictive effects.

A BRIEF HISTORY OF RESEARCH ON SHs

In 1943, Albert Hoffman, a Swiss chemist at Sandoz, accidentally discovered LSD-25 while examining alkaloids from the rye ergot fungus in search of a vasconstricting agent to reduce blood loss during pregnancy. A small amount of the agent came into contact with his skin and he had the first LSD experience. Sandoz began to test this new agent on animals and other Sandoz employees. The testing for toxicity in animals revealed LSD to be safe with no known human toxic dose (LD_{50}). In 1947, the company began marketing LSD as Delysid for two general indications: as a tool to explore the biological basis of psychosis and as an adjunct to psychotherapy. In 1958, after Albert Hoffman isolated psilocybin as the active ingredient in psychedelic mushrooms, psilocybin was also produced and marketed by Sandoz. This began a quarter century of research into the therapeutic applicability of hallucinogen treatment models, with much of the research centered in Europe and the United States. Two treatment models emerged[3]:

1. Psycholytic
2. Psychedelic

The **psycholytic** model came to predominate in Europe where lower doses of SHs (mostly LSD and to a lesser degree psilocybin) were used as tools to activate and enhance the psychoanalytic process by allowing greater access to unconscious material to effect personality changes in disease states such as personality disorders, neurotic spectrum disorders, and psychosomatic illness.

The **psychedelic** model utilized higher doses of the SHs to access novel dimensions of consciousness remarkably similar to mystical states of consciousness, with oneness, illuminative insight, a sense of the sacred, and ecstatic joy as core parts of the experience. This was a new therapeutic model with no previous basis within the field of mental health research, with parallels more toward religion and mysticism. Treatment of substance-use disorders (SUDs) was predominantly studied within this new model.

By the end of the nearly three decades of research, more than 1000 articles were published in the literature and more than 40,000 subjects were included in basic or

therapeutic clinical hallucinogen research.[4] SUDs, mostly alcoholism, were the most studied of any of the psychiatric disorders, followed by psychological and spiritual distress associated with terminal cancer.[5–7] A treatment model that established the parameters of set (psychological frame of mind, intention, excluding participants with major mental illness or family history of such illness), setting (environment/room on dosing days), dose, preparation with therapeutic dyad teams, and integration of the experience was established.

Unfortunately, and perhaps predictably, the use of hallucinogens, in particular LSD, escaped from the human research laboratory and started to be misused by the general public. The adverse psychological effects (ie, anxiety, panic, psychosis) of the substances became apparent with their large-scale use without proper attention given to their unique properties, set, and setting. Their use for sacred intentional purposes in spiritual settings was replaced by abuse in party-like settings. They also came to be linked to politics in the United States and were associated with the counterculture movement. This and the reports of their adverse psychological effects were the main driving forces leading to the passage by Congress of the Controlled Substances Act of 1970 that established the controlled substances schedule system from I to V.[1] All of the SHs were placed in the most restrictive schedule I category, defined as lacking in safety for use under medical supervision, and with a high addictive liability. This effectively ended all clinical research into the therapeutic applicability of hallucinogen treatment models within the mental health field for the next two decades.

LSD AND ALCOHOLISM TREATMENT STUDIES

Overall, the studies looking at the effect of LSD in alcoholism during the 1950s and 1960s varied widely from astonishingly positive results to worsening of the alcoholism, depending on the design of the study, set, and setting of the dosing sessions and the degree to which preparatory and integrative psychotherapy was used. In 1971, Abuzzahab and Anderson reviewed 31 studies from 1953 to 1969 on the effects of LSD on approximately 1100 alcoholics. They were unable to offer any definitive conclusions about the overall efficacy or lack thereof of LSD-assisted therapy for alcoholics because of the overall wide variability in study designs, definitions of alcoholism, outcome measures, and effect of treatment setting. Overall, the vast majority of these studies were poorly designed by strict standards of modern methodologic paradigms to assess clinical efficacy. However, they were able to report in their final tally of results that[8]:

- 75% of participants receiving a single dose of LSD in the controlled studies were "improved" at 10-month follow-up compared to 44% of the controls.
- 58% of the multiple dosing patient were "improved" at approximately 20-month follow-up compared to 54% of the controls.

In 2012, Krebs and Johansen[9] performed a meta-analysis of previous studies examining the efficacy of single-dose LSD treatments for alcoholism that included the best designed trials in terms of randomization and the presence of a control group. Of the 536 adults identified from the 6 trials, 59% of patients in the LSD group were improved (in terms of a reduction of alcohol misuse at the first follow-up meeting) compared to 38% in the control arm ($P = .0003$), and the pooled odds ratio with respect to improvement in alcohol misuse between the LSD and control groups at the first follow-up was 1.96 (95% confidence interval [CI], 1.36–2.84; $P = .0003$). The significant treatment effects between the LSD and control groups on drinking behavior were observed up to 6-month follow-up but were not significant at 12-month follow-up. This suggests that repeated dosing may be necessary to confer longer lasting antidipsotropic effects.

THE NATIVE AMERICAN CHURCH/PEYOTE, THE UNIAO DO VEGETAL/AYAHUASCA, AND ANTI-ADDICTION

Two religious groups are legally allowed to use SHs in the United States as sacraments central to their religious practices: use of peyote (mescaline) by the Native American Church (NAC) and use of ayahuasca by the Uniao do Vegetal (UDV).

The legal use of peyote by the NAC was established under the American Indian Religious Freedom Act enacted by Congress in 1993,[10] and similarly the legal use of ayahuasca by the UDV was established by the US Supreme Court (in a unanimous 8–0 ruling) in 2006. In both religious communities (NAC/peyote; UDV/hoasca) the abuse of alcohol and drugs (ie, cocaine, heroin) is **proscribed**, whereas ongoing use of the SH is **prescribed**.[11,12] For both, ceremonies are conducted specifically to treat SUDs. In both groups, ethnographic and cross-sectional reports suggest low rates of SUDs, sustained abstinence, and no evidence of adverse psychological or cognitive effects in long-term members in both NAC/peyote and the UDV/ayahuasca research populations, suggesting a link between sacramental SH use in religious settings and anti-addictive effects.[13–19]

To truly determine if the peyote- and ayahuasca-based US religions have lower rates of alcohol or drug use disorders, formal epidemiologic inquiry is indicated. If it is indeed found that the rates are lower compared to those in the general population, then the next line of inquiry would be to ascertain potential causal mechanisms. It would be important to consider possible anti-addictive effects of SH itself, either from its biological effects or those related to its psychospiritual or mysticomimetic properties. It is also entirely possible that the effects have nothing to do the SH and are related to other factors such as **proscription** of drugs and alcohol in the NAC or social and spiritual factors related to membership and practice in the religion. Another possibility is some mix of ongoing effects of SH use and the social, spiritual, and communal aspects of the religion that give meaning to the spiritual experiences.

In addition to its use in traditional ayahuasca-based religions, the use of ayahuasca to treat addictive spectrum disorders has spread outside of religious contexts, with a well-known example being **Takiwasi,** a therapeutic community in Peru established by a group of French and Peruvian psychiatrists, psychologists, and anthropologists to treat drug dependence, in particular, cocaine use disorders. In this center, 15 to 20 addicted individuals are treated at one time; both the patients and the healers ingest ayahuasca (syntonic with the shamanic tradition of ayahuasca administration) and the putative treatment mechanisms are related to psychospiritual effects.[11]

CLASSIFICATION OF HALLUCINOGENS

The serotonergic or classic hallucinogens (which exert their hallucinogenic properties by activating the 2AR) can broadly be broken down into two main categories[20]:

1. Indolealkylamines
2. Phenylalkylamines

The **indolealkylamines** have a core structure similar to serotonin and include **tryptamines**, such as dimethyltryptamine (DMT, ie, found in ayahuasca), psilocybin and its psychoactive metabolite psilocin, semisynthetic ergolines or lysergamides (ie, LSD), and iboga alkaloids (ie, ibogaine).

The **phenylalkylamines** have a core structure more similar to that of norepinephrine and include **phenylethylamines**, such as mescaline (from the peyote cactus *Lophophora williamsii*); and the **phenylisopropylamines**, which are amphetamine

derivatives such as 2,5-dimethoxy-4-methylamphetamine (DOM) and MDMA. Note that MDMA is not a classic hallucinogen because it does not directly agonize the 2AR.

NEUROBIOLOGY AND MECHANISMS OF ACTION OF SHs

All of the classic hallucinogens have marked affinity as agonists for the 2AR but also interact to some degree with 5-HT1, -4,- 5,- 6, and -7 receptors. In addition, the semisynthetic ergolines (ie, LSD) display high intrinsic activity at D_2 and α-adrenergic receptors.[21] Ibogaine has the most complicated pharmacodynamic profile of the SHs and interacts with the following neurotransmitter systems[22]:

1. **Serotonergic** effects: 2AR agonist (SH action), presynaptic release, and inhibition of serotonin reuptake pump (MDMA-like properties), 5-HT3 agonism
2. **Glutamatergic**: Noncompetitive NMDA antagonist (similar to PCP and ketamine)
3. **Opioidergic**: μ agonism (opioid-like effects), κ agonism (similar to salvinorum A)
4. **Cholinergic**: Muscarinic agonist, $\alpha 3\beta 4$ nicotinic antagonist.

Converging lines of evidence from pharmacologic, electrophysiologic, and behavioral research in animals strongly suggests that activation of cortical 2AR receptors is the most critical step in initiating a cascade of biological events that accounts for their hallucinogenic properties.[23] In humans, preadministration of ketanserin (a 2AR antagonist) abolishes almost all of the psilocybin-induced psychoactive effects.[24]

2AR activation by SHs modulates prefrontal network activity by causing marked increases in extracellular glutamate levels that account for increased activity of pyramidal neurons, most pronounced in layer V of the prefrontal cortex (PFC).[25,26] Also, activation of 2AR receptors in the medial PFC affects subcortical transmission by increasing the activity of serotonin neurons in the dorsal raphe and dopamine (DA) neurons in the ventral tegmental area (VTA), the latter resulting in increased DA transmission in mesocortical and mesostriatal areas.[27–29] In a human study, psilocybin induced an increase in striatal DA that was correlated with euphoria and depersonalization.[30] This is interesting to note in light of the lack of psilocybin's ability to produce dependence syndromes (see section on Addictive Liability of Serotonergic Hallucinogens).

Imaging studies of SH use on the brain

Human brain imaging studies have demonstrated that psilocybin produces a particular pattern of prefrontal–limbic activation/de-activation[23,31]:

1. Marked prefrontal activation (hyperfrontality): frontomedial, dorsolateral cortices, anterior cingulate, insula, and temporal poles
2. Decreased activation of areas important for gating or integrating cortical information processing such as the bilateral thalamus, right globus pallidus, bilateral pons, and cerebellum
3. Decreased activity in the somatosensory cortical areas, occipital cortex, and visual pathways.

Taken together, psilocybin produces hyperfrontality with divergent prefrontal–subcortical activation in such a way as to increase cognitive and affective processing in the context of reduced gating and reduced focus on external stimulus processing.

Animal models of SH use

In animal models, SHs increase brain-derived neurotrophic factor (BDNF) levels in prefrontal and limbic brain areas. There is also evidence that 2AR agonists activate differing intracellular signaling pathways depending on whether they have hallucinogenic properties or not (ie, lisuride).[32] The 2A receptor is a Gq-coupled G protein–coupled receptor

(GPCR) that responds to the endogenous neurotransmitter, serotonin, whereas the mGluR2 is a Gi-coupled, pertussis toxin–sensitive GPCR that responds to glutamate. It has been demonstrated that 2AR and mGluR2 receptors form a functional heteromeric complex through which classic hallucinogens cross-signal to the Gi-coupled receptor.[33] Furthermore, it was recently demonstrated that the formation of the mGluR2/2AR complex establishes an optimal Gi–Gq balance in response to glutamate and serotonin (increase in Gi and decrease in Gq) and that the classic hallucinogens may produce their pro-psychotic states by effecting decreases in Gi and increases in Gq.[34]

ADDICTIVE LIABILITY OF SHs

A commonality among all drugs that are capable of producing dependence or addictive syndromes is their ability to substantially increase extracellular DA levels in the mesoaccumbens pathway, either directly by enhancing DA transmission through reuptake inhibition or facilitating presynaptic DA release (ie, cocaine, amphetamine, MDMA) or by indirect γ-aminobutyric acid-ergic (GABAergic), cholinergic, or glutamatergic mechanisms that affect DA-cell firing (ie, alcohol, sedatives, opioids, cannabis, nicotine, NMDA antagonists [PCP, ketamine, dextromethorphan]).[35]

In contrast to all other drugs of abuse, SHs are not considered to be capable of producing sufficient reinforcing effects to cause dependence (addiction) syndromes.[36] Animal models (ie, self-administration, conditioned place preference) have failed to reliably demonstrate addictive liability of the SHs, suggesting that they do not possess sufficient pharmacologic properties to initiate or maintain dependence.[32] Almost all of the SHs, with the exception of LSD,[37,38] lack affinity for DA receptors or the DA transporter and do not directly affect dopaminergic transmission. Interestingly, despite evidence that SHs have been shown to increase DA transmission in striatal areas in humans, they fail to significantly activate the nucleus accumbens (NA) in positron emission tomography (PET) imaging studies consistent, with the lack of evidence linking classic hallucinogens with dependence syndromes.[24,30,31]

In fact, in animals, ibogaine (as well as nor-ibogaine and 18-methoxycoronaridine [18-MC]) has been shown to decrease DA efflux in the NA in response to opioids[39–42] and nicotine.[43–45] Furthermore, rapid tachyphylaxis occurs with repeated administration of the classic hallucinogens (with the exception of *N,N*-dimethyltryptamine [DMT]) and with repeated daily dosing, psychological effects disappear within several days, an effect that correlates with and likely is mediated by $5HT_{2A}$ downregulation.[46] In addition to the lack of biological evidence, epidemiologic studies have also failed to reliably demonstrate a link between SHs and their ability to engender dependence syndromes, and the National Institute on Drug Abuse does not consider the SHs drugs of "addiction" because they do not produce compulsive drug-seeking behavior and because most recreational users decrease or stop their use over time.[47,48]

IBOGAINE AND OPIOID WITHDRAWAL; IBOGAINE AND ADDICTION

Ibogaine is a psychoactive indole alkaloid that is the most abundant alkaloid found in the root bark of the Apocynaceous shrub *Tabernathe iboga* in West Central Africa. It has been used for centuries by the Fang peoples as a religious sacrament by the Bwiti and Mbiri tribes (in Gabon, the Cameroons, and the Republic of Congo) as part of a syncretic ancestor-worship religion.[49,50]

Research on ibogaine in the United States began in the early 1960s when a group of lay drug experimenters, led by Howard Lotsof, became interested in the psychotherapeutic potential of ibogaine as an SH. Over the last 50 years, research on ibogaine in animals and humans has demonstrated the following:

- *Heroin withdrawal:* Surprisingly, a heroin-dependent group reported the complete elimination of heroin withdrawal symptoms with a one-time use of ibogaine.[51] Since then, other human anecdotal reports and several case series studies have strongly suggested that ibogaine diminishes or eliminates opioid withdrawal symptoms[52–55] and drug craving for multiple drugs of abuse including opiates, cocaine, and amphetamines.[52,54,56] Furthermore, animal studies have confirmed the anti-addictive properties of ibogaine, demonstrating that ibogaine effectively attenuates heroin, morphine, cocaine, amphetamine, methamphetamine, nicotine, and alcohol-seeking behaviors.[22,40,57]
- *Alcohol self-administration:* In addition, ibogaine has also been shown to inhibit operant alcohol self-administration in rats and to reduce alcohol intake in a reinstatement paradigm.[58]
- *Chronic ibogaine administration:* Despite there being no significant history of ibogaine misuse or abuse in the United States, it was classified as a schedule I agent as part of the Controlled Substances Act in 1970. In animal self-administration paradigms for drug abuse, iboga alkaloids have not been demonstrated to maintain reliable drug self-administration or to produce a withdrawal syndrome after chronic administration.[55,59] In fact, ibogaine has become noteworthy only in the last several decades, during which evidence has begun to accumulate that it may be an effective anti-addictive treatment for a variety of drugs of abuse.

In 1991, NIDA began an ibogaine research project based on case reports and preclinical evidence suggesting its utility. In 1993, the US Food and Drug Administration (FDA) approved a phase I clinical trial of ibogaine that was never completed. Before the research project ended in 1995, NIDA had committed several million dollars in support of its ibogaine research project, in which ibogaine was administered to human subjects in an FDA-approved phase I study.[52] It remains unavailable for use in the United States because of concerns regarding its safety, specifically neurotoxic and cardiotoxic issues. The neurotoxicity of greatest concern relates to possible cerebellar damage, observed in rats but not in mice or primates.[52,60] The cardiac toxicity includes bradycardia and possible other forms of arrhythmia, including possible QT prolongation. Consistent with anthropologic reports of fatalities during initiation rites of the Fang people of West Africa, at least a dozen deaths have been reported within 72 hours of ibogaine use since 1990.[22,61]

The **clinical use of ibogaine** to treat SUDs in a medicalized setting began when Dr. Deborah Mash, a professor of neurology at the University of Miami and ibogaine researcher, set up a medically oriented ibogaine treatment clinic in St. Kitts in the Caribbean in 1996 to treat patients with SUDs and opiate dependence/withdrawal in particular. The clinic administered ibogaine with close cardiac monitoring under the supervision of emergency medicine personnel. The clinic operated for approximately 10 years, but is no longer active.

Currently, despite ibogaine not being officially approved as a therapeutic agent in the United States, it continues to be used in alternative treatment settings, by both lay treatment providers in nonmedical settings and by practitioners in conventional medical settings outside of the United State.[62] A worldwide expansion of ibogaine use to treat SUDs has occurred within the past decade. In an ethnographic study into the ibogaine subculture, Alper and colleagues estimated that as of early 2006, approximately 3400 individuals had taken ibogaine (a fourfold increase relative to 2001) and approximately three-quarters used ibogaine to treat an SUD and about half specifically used it to treat opioid withdrawal.[22] One of the expanded uses of ibogaine

(including in the United States) has been in an underground lay provider treatment setting where nonmedical personnel administer ibogaine illegally and without medical monitoring. Given ibogaine's potential toxicity and link to fatalities, it is of concern that it is being used in such uncontrolled settings.

ANTI-ADDICTIVE MECHANISMS OF CHANGE

Potential Biological Change Mechanisms

Iboga alkaloids and the treatment of acute opioid withdrawal: biological mechanisms

Animal studies have provided strong and consistent evidence for the ability of ibogaine and a synthetic congener, 18-MC, to attenuate opioid withdrawal in rats, mice, and primates,[22] although the evidence has been mixed on the ability of ibogaine to attenuate opioid withdrawal precipitated by naloxone in animals.[63] The ability of ibogaine and related congeners to attenuate or suppress opioid withdrawal is unique among the SHs, with no evidence of other similar agents (ie, LSD, psilocybin, DMT, mescaline) having any efficacy diminishing opioid withdrawal. Regarding the potential of ibogaine to treat acute opioid withdrawal, agonism at the μ opioid receptor has to be considered. The main metabolite of ibogaine, metabolized by cytochrome P4502D6, is noribogaine, which is a strong candidate to account for diminished acute opioid withdrawal symptoms[64] because of noribogaine's longer half-life, full μ agonist effects, and greater μ opioid binding affinity (relative to ibogaine).[63] However, it may be that ibogaine diminishes opioid withdrawal through neuroadaptations related to opioid tolerance or dependence and may do this through modulation of intracellular signaling at the μ opioid receptor.[22] For instance, prior exposure to morphine augments ibogaine's decrease of sensitized DA efflux in the NA in response to morphine administration[65] and ibogaine is known to enhance the antinociceptive effects of morphine.[66]

DA antagonism, the NA, anti-addiction, iboga alkaloids

Increased transmission of DA antagonism in the NA is one of the core hallmark neurobiological features of the addictive process signaling reward/pleasure/reinforcement and beginning the process of neuroplasticity and associative learning between previously neutral stimuli that come to predict drug-seeking behavior in individuals who develop addictive spectrum disorders.[67] Accordingly, based on this, a traditional anti-addictive approach involves blocking DA activity in brain reward pathways (ie, NA) by either preventing delivery of the addictive agent to the receptor site (ie, vaccines) that mediates the drug's addictive liability, using DA receptor antagonists, or using antagonists that block a particular addictive mediating receptor.

In animal models, ibogaine, noribogaine, and 18-MC are known to decrease DA efflux in the NA in response to opioids[39–42] and nicotine.[43–45] The ability of iboga alkaloids to diminish DA activity in the NA therefore strongly suggests an acute anti-addictive property, whatever may be the specific mechanism by which this effect occurs.

DA agonism, the NA, anti-addictive effects, SHs

Although blocking DA mesolimbic reward circuitry has been traditionally studied in the development of pharmacotherapeutic interventions for addictive syndromes, a new line of inquiry involves activation of this circuitry. Blum and colleagues have coined the term *reward deficiency syndrome* to describe a genetically related hypodopaminergic syndrome at the level of the NA caused by genetic polymorphisms in the 2AR, D2 (DA D2 receptor), and catechol-*O*-methyl-transferase (COMT) receptors associated with impulsive, compulsive, and addictive behaviors.[68] This may

relate to the well known genetic contribution to addictive syndromes, estimated to account for at least 50% of the risk of developing an addictive syndrome.[69] Irrespective of whether this hypodopaminergic state in the mesolimbic pathway in individuals at risk for addiction exists as a risk factor for addiction, it certainly develops temporally with dependence syndromes. Two effects that likely contribute significantly to the addicted state are[70]:

1. Changes in midbrain DA
2. PFC DA and glutamate function.

Damage to the DA system is one of the changes that likely contributes to the transition from abuse to dependence syndromes and is associated with decreased DA receptor density and release in the NA and PFC, diminishing the ability of DA to signal novel salient events, leading to underexcitability to biologically relevant stimuli.[71] Preclinical and animal studies have suggested that persistent low-grade stimulation of DA D2 receptors (by D2 agonists) can induce a proliferation of these receptors rather than downregulation,[72–74] which is interesting in light of evidence that low DA D2 receptor levels are associated with addictive behaviors in humans.[75,76]

In addition to the aforementioned anti-addictive approach of DA antagonism at the NA, another traditional approach is that of **agonist substitution** or replacement therapy in which an addictive agent is replaced with one that has less addictive liability based on pharmacodynamic and pharmacokinetic characteristics such as:

- Receptor potency/affinity (ie, agonist, partial agonist, antagonist)
- Rate of central nervous system (CNS) absorption (ie, slower rates of absorption associated with less addictive liability)
- Half-life (ie, receptor, distribution, elimination with longer duration preferable).

Examples of this approach with a substantial evidence base for anti-addictive effects include methadone and buprenorphine for opiate use disorders and nicotine replacement and varenicline for nicotine use disorders.[77] Agonist substitution partially works in a similar way to the aforementioned antagonism approach. By occupying a particular addictive mediating receptor (ie, μ opioid, nicotinic acetylcholine receptor [NAR]), an agonist will functionally antagonize a more addictive drug of abuse (ie, heroin/μ opioid receptor; inhaled nicotine/NAR) and prevent it from binding and activating the receptor leading to surges in DA in the NA associated with the initial rewarding effects and long-term damage and downregulation of DA neurons. Alternatively, these agonist substitution approaches may work similarly to the aforementioned approach of persistent low-grade stimulation of D2 receptors leading to upregulation and restoring normal functioning of these receptors to re-respond normatively to biologically oriented rewards and novel stimuli.

In trying to now tie this to potential anti-addictive properties of the SHs, it is important to reiterate that the SHs increase DA transmission in mesolimbic reward areas (except ibogaine which, as mentioned previously, decreases DA transmission) without causing dependence syndromes. Is it possible that these agents could induce low-grade DA transmission that could lead to regeneration of D2 receptors and restore them to normative functioning? If this were to be possible, it is unlikely that an acute time-limited effect on the order of several hours would be enough to engender prolonged anti-addictive change. Either repeated dosing or a longer-term biological process would have to be invoked for this to be plausible.

Hallucinogens and Potential Long-Term Anti-Addictive Biological Processes

5-HT$_{2A}$ downregulation

One type of neuroplastic change caused by classic hallucinogens is their ability to produce rapid downregulation and desensitization of cortical 2ARs (especially anterior cingulate and frontomedial cortices) in rats in response to a variety of agents including LSD, 2,5-dimethoxy-4-bromoamphetamine (DOB), 2,5-dimethoxy-4-iodoamphetamine (DOI), and DOM.[46,78–80] Furthermore, frontolimbic 2AR density correlates positively with increased anxiety and an exaggerated stress response in humans.[81] Given that anxiety and stress (mediated by increased activation of the stress response system (ie, corticotropin releasing factor, cortisol)} are significantly involved in the relapse process,[82] it is possible that 2AR downregulation by classic hallucinogens could alter and diminish stress-induced substance use relapse.

Neurotrophic factors altered by SH

Another interesting area of longer-lasting effects of SHs relates to their ability to alter the expression of neurotrophic factors. Both BDNF and glial cell line–derived neurotrophic factor (GDNF) expression can facilitate or inhibit addictive behaviors in rats based on the drug type, brain site (ie, cortical or subcortical), and phase of addiction (ie, initiation, maintenance, abstinence/relapse). In addition, SHs have been shown in animals to increase cortical and subcortical levels of BDNF.[83,84] In terms of BDNF's anti-addictive effects, activating BDNF signaling in the dorsal striatum consistently decreases alcohol intake and self-administration. Regarding cocaine, activating BDNF signaling in the medial PFC diminishes cocaine-seeking behaviors while activation of BDNF signaling in the NA has opposite effects.[85]

Drug-craving reduction An interesting aspect of ibogaine treatment seems to be its ability to reduce drug craving for extended periods of time even after a single treatment. Anecdotal reports in humans with a single treatment have suggested that drug craving can be reduced ranging from several weeks to up to 6 months.[64] Animal studies have confirmed this as well; single treatments with ibogaine were able to induce extended periods of reduced cocaine self-administration[40,57] and a diminution of ethanol intake for up to 48 hours.[58]

From a neurobiological perspective, it is known that long-lasting structural and molecular alterations in dopaminergic neurons in the mesolimbic pathway result from neuroadaptative changes related to chronic drug or alcohol exposure and that a subset of these alterations can be reversed by activation of the GDNF signal pathway.[86]

Upregulation of GDNF pathway It has recently been suggested that upregulation of the GDNF pathway in the midbrain may mediate the anti-addiction properties of ibogaine. He and Ron, using a dopaminergic-like SHSY5Y cell line, observed that short-term ibogaine exposure resulted in a sustained enhancement of GDNF expression, mediated by induction of the long-lasting autoregulatory cycle by which GDNF positively regulates its own expression.[87] These findings strongly suggest the need for further research into possible clinical applications of agents, such as ibogaine, that can enhance GDNF functioning as a way to harness a novel anti-addiction pharmacotherapeutic strategy.

Translating anecdotal findings into supervised clinical setting Further research into the potential use of ibogaine with addictive disorders should continue with the goal of translating the anecdotal and preclinical findings into the supervised clinical setting as

well as further characterizing its anti-craving mechanisms. Moreover, it would be important to use iboga alkaloid compounds that confer the therapeutic effects while minimizing or eliminating the toxic side effects. One such potential agent to consider is 18-MC, a synthetic ibogaine congener designed specifically for this purpose and without any psychoactive properties.[88] The anti-addictive properties of 18-MC are currently being studied at NYU and NIDA (K.R. Alper, personal communication, 2011).

Glutamatergic homeostasis: neuroplasticity

As addiction progresses, the neurocircuitry of the reward pathway becomes corrupted, reorganized, and dysregulated whereby the behavioral system changes from a DA-oriented one in the NA (involved in the acute high-salience attribution of novel stimuli and the initiation of learning and conditioned responses) to a glutamate-based system in the PFC (especially the anterior cingulate and orbitofrontal cortex) marked by altered glutamatergic transmission in projections from the PFC to the NA.[89] Specifically, there is an increased glutamatergic modulation of accumbens DA cell reactivity in response to drug-related cues and a decreased response to biologically oriented natural rewards.[90] Moreover, impaired plasticity (ie, long-term potentiation and long-term depression) has been demonstrated in animals in communication between the PFC and the NA that is thought to limit the ability of dependent individuals to make behavioral and motivational changes (ie, attend to natural rewards, novel stimuli, learn new conditioned associations) to compete with drug-seeking stimuli and behaviors.[90] Based on this glutamate homeostatic dysfunction model in functional connectively between the PFC and the NA in the addicted state, a new line of pharmacotherapeutic interventions centered on glutamatergic modulation is emerging and there is evidence in animals for promising therapeutic targets of restoring synaptic plasticity such as restoring the activity of cysteine–glutamate exchangers, glutamate transporters, and enhancing the NMDA receptor function.[91]

Given that SHs increase extracellular glutamate levels and activity in the prefrontal–limbic circuitry, it is possible that a normalization in functional connectivity in this network though a glutamate-dependent neuroplastic adaptation could produce an anti-addictive effect. One possible mediating mechanism might be through increased signaling in BDNF because, as mentioned previously, SHs increase BDNF transmission, which is related to decreased alcohol self-administration in the dorsal striatum and diminished cocaine-seeking behaviors in the medial PFC in animals.

Gene transduction

Multiple studies have now confirmed that 2AR activation alters gene expression, in particular in PFC regions. Increases in gene expression of the following genes have been identified: c-*fos*, arc (activity-regulated, cytoskeletal-associated protein localized in neuronal dendrites), *ania3* (involved in glutamate signaling), *EGR-1* (early growth response protein 1 endogin, a zinc-finger transcription factor), *EGR-2*, period-1 (a circadian rhythm-related gene), and *Beta-arrestin 2*.[23,32] How this might related to conferring anti-addictive effects is unknown.

CURRENT STATE OF RESEARCH IN THE UNITED STATES ON SEROTONERGIC HALLUCINOGEN TREATMENT MODELS FOR SUBSTANCE ABUSE

If research were undertaken to examine the therapeutic utility of hallucinogen-assisted treatment models for SUDs, what would be the essential elements to consider in the study design? Charles O'Brien has outlined the essential ingredients: specific diagnoses and validated psychometric diagnostic instruments (ie, structured clinical interview for DSM-IV [SCID]), randomization, placebo control, use of specific

diagnoses using validated measures, inclusion of severity measures, informed consent to clearly inform the participant of the unique psychological risks and benefits of these drugs, placebo control, random assignment, the use of objective blind raters, clearly defined substance outcomes (ie, abstinence vs use reduction), the need for adequate follow-up, and a standardized dose of manual guided psychotherapy with adequate supervision.[92]

In addition, it would see key to assess other factors such as stage of illness, typology of illness, motivation for change, social support, and psychiatric and medical comorbidity. Attention to therapist training, fidelity of dyad treatment teams, and the nature of the preparatory versus integrative psychotherapy would have to be considered carefully as well. The setting of dosing sessions would have to be carefully constructed so as to resemble more of a comfortable living room–like setting with flowers, fruit, music, and personal and meaningful items of the participants so as to create a safe, comfortable environment that is more likely to occasion a mystical experience as opposed to a cold clinical type typical hospital-based setting that would be less likely to occasion such an experience and might be more likely to produce negative and adverse psychological effects. Eyeshades and focusing internally might also be important to consider to more likely occasion a mystical experience. Single versus multiple dosing paradigms would need to be considered. Importantly, it would be key to consider the type of psychotherapeutic/behavioral platform or container that would be utilized in these studies. One could consider motivational techniques that are not intrinsically spiritually oriented such as motivational interviewing (MI) or employing those that are spiritually oriented in nature such as 12-step facilitation (TSF) or mindfulness-based relapse prevention (MBRP).[93,94]

Single Versus Multiple Dosing Paradigms: Electroconvulsive Therapy Model

It would be naïve to think that a one-time experience with a hallucinogen, however profound or mystical in nature, could affect long-term sobriety in addicted individuals, especially without linkage to aftercare and psychosocial treatment. In some addicted individuals, a spiritual conversion experience can last a lifetime. However, the vast majority of patients with dependence syndromes need multiple repeated treatment attempts including with 12-step modalities. So, it may be that repeated dosing is necessary, similar to an electroconvulsive therapy (ECT) type model. On a psychological level it may be that incremental changes in motivation initiated by a psycholytic experience can be combined with psychosocial motivational interventions to gradually increase motivation for abstinence or use reduction. In this model, repeated dosing sessions combined with added motivational psychotherapies may be needed to continue the momentum of the change process. Alternatively, it may that a mysticomimetic experience causes a pronounced and sudden quantum change toward abstinence that is maintained with relapse prevention but then relapse occurs within a short period of time (ie, within weeks to several months). In this model, repeated dosing sessions may be needed to reignite motivational changes once they regress or to maintain motivation for sobriety and recovery as part of relapse prevention.

From a biological perspective, it may be that repeated dosing is necessary to sustain long-term changes that can account for prolonged anti-addictive molecular or genetic processes. As mentioned previously, some possibilities have to do with alterations in signaling in BDNF and GDNF and through glutamate-dependent neuroplastic adaptations that may restore functional connectivity between prefrontal cortical and limbic reward structures.

As mentioned in the early LSD alcoholism research, there appeared to be a treatment effect in the better designed controlled studies but it tended to be short

lived, on the order of several months, suggesting the utility of a multiple dosing paradigm study design.[9,95]

Active Hallucinogen Treatment Studies

Currently, in the United States, there are several active or near-active hallucinogen treatment studies for SUDs:

- Johns Hopkins has an active pilot study examining the efficacy of psilocybin-assisted CBT for smoking addiction. A small sample (N = 4) has been successfully treated so far with long-term abstinence in all, with biologic markers showing no signs of active smoking (Johnson M, personal communication, 2012).
- Columbia University and the New York State Psychiatric Institute have an active controlled trial of ketamine-assisted MBRP for cocaine dependence. Several subjects have completed the trial, also with early promising signs of increased abstinence (Dakwar E, personal communication, 2012).

There are two studies in the early phases of approval examining repeated dosing of psilocybin-assisted psychotherapy to treat alcohol use disorders.

- At the University of New Mexico, a study examining psilocybin-assisted motivational interviewing is in an active phase of approval (Bogenschutz, personal communication, 2012).
- At NYU, a controlled trial of psilocybin-assisted psychotherapy to treat alcohol dependence will utilize a combination of MI and 12-step facilitation therapies (Ross S, personal observation, 2012).

It is worth noting that although all of these studies undergo rigorous governmental (ie, FDA and Drug Enforcement Administration [DEA]) and local (ie, institutional review board [IRB], Clinical Translational Science Institute [CTSI]) review processes and schedule I licenses are being granted for clinical research in academic medical centers, the funding for these studies comes largely from private foundations. The exception to this is the aforementioned ketamine-MBRP study funded by the National Institute on Drug Abuse as part of a K award.

SUMMARY

Only time will tell if serotonergic hallucinogen-assisted psychotherapy treatment paradigms for SUDs will prove to be safe and effective in double-blind, placebo-controlled clinical trials. If they are, they would truly constitute a novel psychopharmacologic–psychosocial treatment paradigm to treat addictive disorders, although the risk of adverse psychological events would have to be controlled through a careful screening process and the risk of misuse of the substances or developing use syndromes would have to be considered, although the overall risk would be low because, as mentioned, SHs are unlike all other drugs of abuse in that they do not appear to produce dependence syndromes. There effects on the NA and DA range from inhibition to slight activation, all this without producing addiction. The ability of these medicinal tools to treat a range of addictive, psychiatric, and existential disorders is remarkable in scope and possibility. They truly represent a potential paradigmatic shift within the field of psychiatry, too interesting to not explore further.

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