Chapter

An Evaluation of Diverse Therapeutic Interventions for Substance Use Disorders: Serotonergic Hallucinogens, Immunotherapy, and Transcranial Magnetic Stimulation

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Abstract

Substance Use Disorders are a substantial public health concern whose treatment remains challenging. High rates of relapse are in fact a hallmark of drug addiction despite the wide variety of psychotherapeutic and pharmacotherapeutic approaches. This chapter discusses three innovative and controversial therapeutic approaches for Substance Use Disorders that have received considerable attention: the use of classic serotonergic hallucinogenic drugs (LSD and psilocybin), addiction immunotherapy and anti-addiction vaccines, and the use of transcranial magnetic stimulation. These treatments are not necessarily new but are discussed because they represent a diverse set of approaches that address varied aspects of drug addiction. Furthermore, they have an accumulated body of research from which to assess their future viability. For each of these therapeutic approaches this chapter considers the theoretical basis for use, history, status of the literature supporting their use, limitations, and potential applications. While these three interventions represent highly varied approaches to the treatment of Substance Use Disorders, this diversity may be necessary given the complex nature of addictive disorders.

Keywords: Pharmacotherapy, hallucinogens, addiction vaccines, addiction immunotherapy, transcranial magnetic stimulation

1. Introduction

Substance Use Disorders (SUDs) are likely to be chronic conditions for many effected individuals [1, 2] and are associated with a variety of negative physical and psychological health outcomes [3, 4]. Among those treated for drug and alcohol dependence, 40–60% relapse within a year of treatment cessation [5, 6]. Longitudinal cohort studies have demonstrated significant relapse rates across a variety of substances and yielded insight into predictors of remission and relapse. A recent meta-analysis of 21 long-term remission studies, conducted between 2000 and 2015, examined follow-up periods with a minimum of three years or reported

lifetime remission. The results showed 35–54% achieved remission after a mean follow-up of 17 years. Moreover, the pooled estimated annual remission rates suggested yearly remission was uncommon ranging between 6.8% and 9.1% [2]. The conclusion that SUDs are likely to be long-term in nature is consistent with studies likening them to other chronic diseases and highlights the need for treatment to address the chronicity of SUDs [5].

Despite the poor long-term prognosis of SUDs, research suggest treatment is often efficacious in the short-term [7] as well as able to positively affect the long-term outcomes [7, 8]. Multiple longitudinal cohort studies support the efficacy of a variety of therapeutic approaches while at the same time revealing significant heterogeneity of treatment responsivity. For example, individuals treated for Alcohol Use Disorders (AUDs) via Alcoholics Anonymous (AA), formal treatment, or a combination of the two are more likely to be abstinent after 8 years than untreated individuals, however the AA only group surpassed the formal treatment group at 1- and 3-year follow-ups [9]. Another study of adults with AUD, most of whom were entering treatment, revealed five trajectory classes distinguished by their changes in drinking patterns across three years with AA involvement predicting abstinence and/or declines in drinking over time [10]. A recent prospective longitudinal cohort study examining heroin use and treatment utilization over 10–11 years also identified five trajectory groups related to treatment utilization and continued drug use [8].

Addiction is fundamentally a brain disease in which chronic use of substances produce neuroplastic changes across multiple brain systems rendering a person more vulnerable to drug craving, escalating use, and relapse. Depending on the effected system, these changes yield increased incentive salience towards the drug and drug associated cues, attenuated reward, motivation, emotion, and altered stress responsivity. These changes are also coupled with deficits in the prefrontal

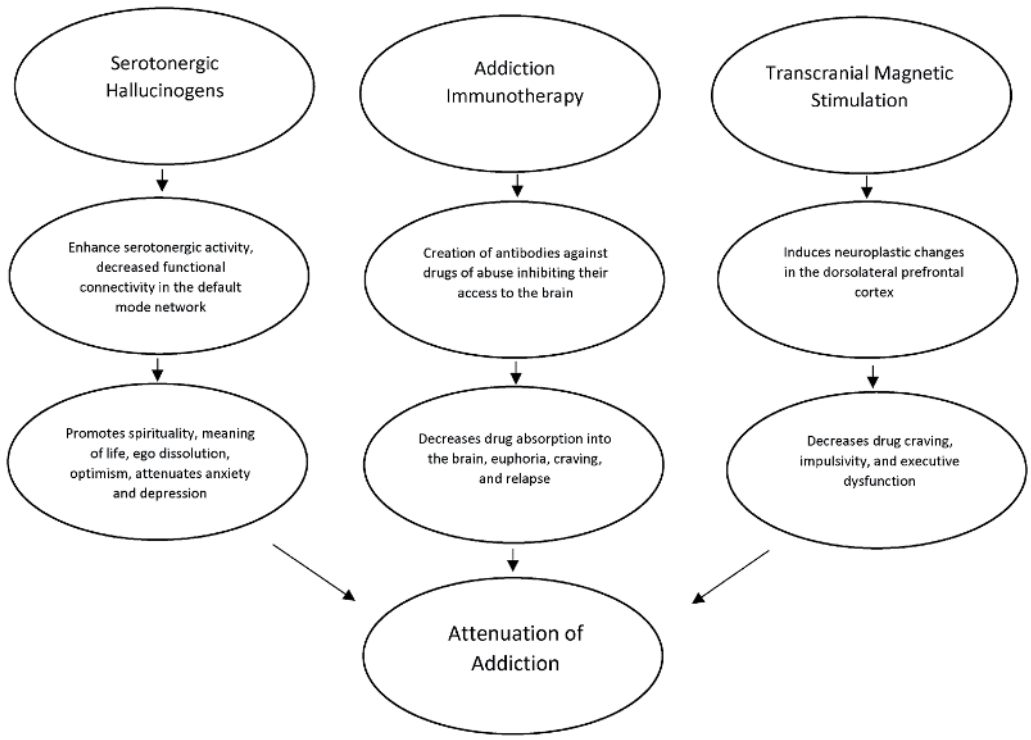

Figure 1.
Therapeutic interventions under development and their putative mechanisms of action (second row from top) and posited anti-additive effects (third row from the top).

cortex and related circuitry leaving drug addicted individuals with diminished executive function and enhanced impulsivity. Moreover, the extent to which these neural adaptions change over time appears to vary, but many have been shown to be highly durable. These neural changes must also be considered within the context of an individual's genetic and epigenetic vulnerabilities, and life circumstances [11–13]. The complexity of variables which contribute to the development of SUDs make them particularly challenging to understand and treat, but they also offer a bevy of targets to develop new treatment approaches.

The purpose of this chapter is to examine three putative treatments for SUDs: serotonergic hallucinogens, immunotherapy approaches, and transcranial magnetic stimulation [TMS]. These treatments are not necessarily new but were chosen because they represent a diverse set of approaches that address varied aspects of drug addiction (see **Figure 1**). Moreover, they have an accumulated body of research from which to assess their future viability. For each of these therapeutic approaches this chapter will address the theoretical basis for use, history, status of the literature supporting their use, limitations, and potential applications.

2. Serotonergic hallucinogens and substance use disorders

Hallucinogenic drugs represent a diverse set of naturally occurring and synthetic substances which vary based on their pharmacological actions and psychoactive effects. The term hallucinogen typically refers to a drug that produces perceptions in the absence of sensory stimuli. However, it is now recognized that hallucinogens produce a broader range of effects across cognition and mood and that hallucinations themselves are less common than the perceptual illusions and sensory distortions they produce. For this reason, the term psychedelic, or mind manifesting, is often used to describe this class of drugs [14, 15]. This section of the chapter focusses on lysergic acid diethylamide (LSD) and psilocybin, two hallucinogens typically referred to as classic serotonergic hallucinogens because they act primarily as agonists on the serotonin (5-HT) 2A receptor and share behavioral effects and proposed therapeutic mechanisms [14].

Psilocybin occurs naturally in more than 200 species of mushrooms and has long been consumed by indigenous cultures to engage with the spiritual world [16, 17]. Albert Hofmann isolated psilocybin and its active metabolite psilocin and subsequently synthesized them in 1958 [18]. LSD was first synthesized in 1938 by Hofmann from ergotamine, a compound found in ergot fungus. After preclinical administration failed to reveal many observable effects in laboratory animals its psychoactive properties were recognized following an accidental ingestion of the drug by Hofmann in 1943. Beginning in the mid-1950s LSD and psilocybin were widely distributed under the names Delysid and Indocybin for study of multiple psychological disorders resulting in more than 1000 papers, treating more than over 40,000 individuals by the mid-to-late 1960's [16, 18–20].

The main focus of research through the late 1960s on the efficacy of hallucinogens in the treatment of addiction was the ability of LSD to attenuate alcoholism [21]. Among the first studies was that of Hoffer & Osmond [22] who followed 24 treatment resistant alcoholics. After taking several weeks to establish a psychotherapeutic relationship, participants were administered a single dose of 200–400 micrograms of LSD while accompanied by a nurse and/or a psychiatrist and in many cases, efforts were made to create a therapeutic environment. The next day, participants were asked to write about their experience. Six participants were considered much improved (complete abstinence and positive lifestyle changes) and another six improved at the conclusion of the study [22].

This early research was influential in establishing a treatment model referred to as "psychedelic therapy" [22], though over time the nature of treatment sessions has varied greatly [21, 23]. Central to this therapeutic approach is the idea that patients will experience a psychedelic peak characterized by an ecstatic state, visual hallucinations, a loss of boundaries between the individual and the objective world, feelings of unity with others, nature, God and the universe [19, 21]. The result of this peak being the induction of a mystical experience that would profoundly alter the way a person views themselves and the world [20]. The dramatic nature of this experience is then interpreted with the assistance of a trained therapist who helps the patient appreciate the psychotherapeutic benefits of the experience [24].

In the following years more than 20 studies with larger sample sizes were published illustrating the effectiveness of LSD for treating alcoholism with many describing unprecedented levels of success [19, 25]. From, 1954–1960 Osmond and colleagues studied the effects of LSD on approximately 2000 alcoholics finding almost half were abstinent after a year [26]. However, by and large this body of research suffered from significant methodological flaws among them a lack of diagnostic specificity, non-random assignment of participants, lack of control and or placebo groups, inconsistent participant follow-up, participant attrition, absence of blind raters, and a lack of clarity in assessing treatment efficacy. Despite these flaws, these early findings were encouraging enough that by the late 1960s six alcoholism treatment programs in North America used LSD based therapy [19, 23, 25].

Gradually some of the methodological problems that plagued earlier studies were partially addressed and a meta-analysis was conducted of six randomized controlled studies (five of which were double-blind) between 1966 and 1970 examining the efficacy of LSD in the treatment of alcoholism [27]. Across these studies 536 adults suffering from alcoholism were compared to 211 control participants receiving a low-dose LSD, d-amphetamine, ephedrine sulphate or non-drug control. While the characteristics of LSD sessions and follow up varied considerably, the results supported the efficacy of a single dose of LSD. Decreases in alcohol misuse were observed at 2–3 and 6 months, but not 12 months post-treatment. Moreover, in three studies reporting total abstinence from alcohol, LSD showed benefits 1–3 months after discharge from treatment programs. Despite these results, research examining the utilization of LSD for alcoholism stalled by the late 1960s due to increased recreational use, its association with the drug counterculture movement, increased restrictions on human drug research, continued methodological concerns, ambiguous results, and passage of the Controlled Substances Act of 1970, which placed LSD in the most restrictive category of drugs [15, 18, 25, 28].

After a cessation of almost 30 years, controlled studies in humans using hallucinogens resumed in the late 1990s [18, 24]. However, Psilocybin, not LSD, emerged as the drug of choice to study the effects of hallucinogens on SUDs [18, 23, 24]. Multiple reasons have been put forward for psilocybin's emergence in this context. Psilocybin has a shorter duration of action compared to LSD, and psilocybin is believed to have a milder side effect profile producing less anxiety, affective disturbances, and milder vegetative side effects [16, 28]. Also, LSD may still suffer from its negative counterculture reputation of the 1960s and a litany of mass media misinformation including exaggerated claims of drug-induced insanity, chromosomal damage, and other falsehoods [14, 15]. In contrast there is growing interest in certain locales to legalize psilocybin's use in licensed facilities for mental health purposes and decriminalize it in others [29].

Among the limited number of recent studies is a small open-label trial with psilocybin for AUD [30]. Psilocybin was administered to 10 alcohol dependent individuals in context of a 12-week program of motivational enhancement therapy. Participants were initially administered 0.3 mg/kg of oral psilocybin followed by

a second dose of 0.3 or 0.4 mg/kg, 4 weeks later. The two doses of psilocybin were separated by four therapy sessions and the final dose was followed by another four sessions. Following the initial psilocybin treatment self-reported alcohol use significantly decreased and remained below baseline at a 36-week follow-up. In addition, significant correlations were reported between the overall intensity and mystical quality of psilocybin sessions and reductions in the percent of drinking days, alcohol craving, and self-efficacy to abstain.

Research examining psilocybin's ability to treat nicotine addiction is also promising. An open-label study was conducted with 15 treatment-resistant, nicotine dependent participants administered 2–3 moderate and high doses of oral psilocybin integrated within a 15-week cognitive behavioral therapy program. Using biologically based verification procedures at a 6-month follow-up 80% of participants were abstinent, at 12 months 67% remained nicotine free, and at 16 months 60% were abstinent. After a long-term follow-up averaging 2.5 years, 75% of study participants were verified as nicotine free. Moreover, participants abstinent at 6-months scored higher on measures of mystical experiences following psilocybin compared to those who relapsed. Greater mystical-type experiences following psilocybin administration also correlated with reduced nicotine cravings at 6 months. At the 12-month follow-up participants rated their psilocybin experience among the 5 most personally meaningful and spiritually significant of their lives [31, 32].

A variety of additional factors speak to the potential viability of serotonergic hallucinogens for the treatment of SUDs. A single or a limited number of drug administrations during supervised treatment sessions may negate a number of liabilities associated with other pharmacotherapies such as high cost, problems with medication adherence, drug interactions and side effects [24]. LSD and psilocybin have a limited addictive liability as indicated by a lack of drug self-administration by laboratory animals [28, 33], relatively slow onset of effects after oral administration not typically characterized by pleasure or craving and has no direct effects on the brain dopamine pathways [15]. Physical withdrawal symptoms do not develop even following prolonged use of LSD and psilocybin and the rapid development of dramatic tolerance, on the order of days, does not facilitate the acquisition of addictive behavior [14, 33]. Methodological details associated with the use of psilocybin for treatment of SUDs can be found in several sources [21, 31, 33].

The general public's perception that psychedelic drugs are dangerous, contradicts the fact that from a physiological perspective they are among the safest classes of drugs [15]. Both drugs are not without their liabilities [14, 15, 28, 33], yet substantial toxicity has only been associated with a small number of users [28] In the context of clinical use, the incidence of problems is substantially mitigated as patients are typically prescreened for psychotic symptoms and cardiovascular issues, receive a single or a small number of doses, pharmacotherapies may be available to reverse untoward effects, and therapeutic sessions are supervised by a trained clinician [24, 34]. Recent trials examining the efficacy of these hallucinogens for SUDs have reported no serious adverse effects [30–34] nor have trials examining these hallucinogens in patients with anxiety, depression, or healthy volunteers [18].

A variety of mechanisms have been suggested to explain the therapeutic efficacy of LSD and psilocybin for SUDs and many overlap with proposed explanations for addressing other psychological disorders [18, 34]. Depression and anxiety are hallmarks of addiction [17]. Both negative affective states have been shown to be ameliorated following LSD and psilocybin administration [18, 19, 34] and are linked to prolonged increases in optimism and wellbeing [17]. While it cannot be ruled out that these drug's effects on mood and anxiety are part of a broader mechanism, the fact that antidepressants [35] and anxiolytics [36] alone are generally not

effective treatments for managing SUDs suggest this represents at best an incomplete explanation for hallucinogens therapeutic effects for SUDs.

It has been widely suggested that LSD and psilocybin's experiential effects underly their benefits for treating SUDS [17]. Alcoholics Anonymous has long argued that addiction follows from deficits in spirituality and meaning [37]. Bill Wilson one of the co-founders of Alcoholics Anonymous, credited his experiences with hallucinogens as the reason for his own abstinence and advocated for LSD as a pathway to sobriety [38]. Spirituality has been demonstrated to play a role in the success of Alcoholics Anonymous [39] and other therapeutic approaches [40] and a sense of purpose in life decreases chronic heavy drinking [10]. The benefits of hallucinogenic-based therapeutic experiences may also lie in their intensity [17] as their effects are often described as life changing in nature [31, 32] and research has shown users who experience the most profound mystical experiences consistently undergo the greatest symptom relief [15]. Moreover, stronger mystical experiences and greater intensity of subjective effects of psilocybin are associated with alcohol and nicotine abstinence suggesting a mediating role of mystical experience in psychedelic-facilitated addiction treatment [30, 41].

Consistent with the importance of hallucinogen induced experiential effects recent research using brain imaging in healthy volunteers has shown LSD and psilocybin decrease functional connectivity in the default mode network (DMN), a pathway bilaterally spanning the medial and lateral parietal, medial prefrontal, and medial and lateral temporal cortices, and whose activity appears augmented in depressed patients [24, 42, 43]. Moreover, administration of both drugs was associated with "ego-dissolution" and "altered meaning" suggesting the importance of this circuit for the maintenance of "self" or "ego" and its processing of "meaning" [43, 44]. These results and those of other studies support the idea that classic hallucinogens may function to increase processing of positive stimuli and decrease processing of negative stimuli, elevate mood, and decrease coupling of neural networks allowing for unrestrained exploration of spirituality and meaning [21, 24]. Imaging studies of this network in those with SUD following administration of hallucinogens and after periods of abstinence are needed.

It is noteworthy that past and present research examining the efficacy of LSD and psilocybin in combination with psychotherapy for the treatment of SUD has been consistently promising [18]. Their benefits compare favorably with daily administration of naltrexone, acamprosate, and disulfiram for the treatment of AUD [27] and exceed success rates of behavioral and pharmacological interventions for nicotine dependence [31]. In addition, this approach represents a sea change in the dramatic, broad, and long-lasting nature of its effects and appears relatively safe when administered in a clinical setting. Recently a therapeutic model specifically for psilocybin-assisted treatment of AUD has been proposed [21], as have a neuroscience based mechanistic theory of explaining psilocybin's efficacy for treating SUD [28], and larger randomized studies are now being conducted on the efficacy of psilocybin for AUD, nicotine, and cocaine dependence [34, 45]. However, the above advances should be tempered with the knowledge that recent research has had small samples, this approach is demanding on both the patient and therapist, hallucinogens and hallucinogen-assisted psychotherapy have a negative reputation and are misunderstood by many [24, 45, 46].

3. Addiction immunotherapy: anti-addiction vaccines

The primary immunotherapies being developed for SUDs are vaccines that cause the generation of antibodies directed against drugs of abuse such as cocaine,

nicotine, and opioid analgesics. The underlying rationale is that once drugs of abuse are bound to antibodies, the resulting complex is too large to cross the blood–brain barrier. This reduces the amount of abused substance that reaches the central nervous system (CNS) and thereby reduces the rewarding effects of the drugs. The development of vaccines for drugs of abuse is complicated by the fact that the drugs themselves are small molecules that do not inherently elicit an immune response. To overcome this obstacle, drug molecules or their derivatives (haptens) are typically attached to an immunogenic carrier molecule and administered with adjuvants to stimulate the generation of antibodies directed against the drug. Vaccine candidates have been developed against several drugs of abuse using variations on this approach [47].

Cocaine abuse represents a condition for which a vaccine could be of particular use since there are currently no approved pharmacotherapies to promote abstinence or prevent relapse. Studies in the 1990s conducted in rodents demonstrated that anti-cocaine vaccines could induce the generation of cocaine-specific antibodies and reduce cocaine levels in the brain following peripheral cocaine administration [48, 49]. Additionally, vaccination reduced the psychostimulant (locomotion and stereotopy) effects of cocaine in rats [48], and vaccination or the administration of monoclonal antibodies against cocaine reduced cocaine self-administration and the reinstatement of cocaine self-administration following extinction in rats [49, 50].

Two cocaine vaccines are currently listed on ClinicalTrials.gov. The vaccine that has been most studied is the TA-CD vaccine. This vaccine, which consists of succinylnorcocaine (SNC) attached to a recombinant cholera toxin B (rCTB) carrier administered with aluminum hydroxide adjuvant, caused the generation of cocaine-specific antibodies in rats and reduced cocaine self-administration [51]. The results of a randomized, double-blind, placebo controlled, Stage I clinical trial in which 34 former cocaine abusers in a residential treatment facility were randomized to receive three vaccine injections during the first two months of the study at doses of 13, 82 or 709 mg or an equivalent number of placebo injections (n = 6) indicated that the vaccine was well tolerated and elicited the dose-dependent production of cocaine-specific antibodies which peaked after the third injection and declined over the remainder of the year-long study [52]. A subsequent open-label, outpatient, treatment study involving 18 cocaine-dependent participants indicated that participants who received a total of 2000 mg of vaccine administered in five equal injections over 12 weeks achieved higher mean peak antibody titers and reduced cocaine use over 12 weeks relative to participants who received a total of 400 mg of vaccine administered in four equal injections over 8 weeks [53]. The majority of participants who did use cocaine during the study reported a reduction in the euphoric effects of the drug. The results of a subsequent study conducted in a laboratory setting with participants who were actively abusing cocaine indicated that participants with immune responses to the TA-CD vaccine above the 50th percentile reported reduced positive subjective effects of smoked cocaine [54].

The results from a 24-week Phase IIb clinical trial conducted with 115 cocaine- and opioid-dependent participants enrolled in an outpatient methadone program found that participants who mounted a robust antibody response ($\geq$43 mg/ml) following five vaccine injections (360 mg each) administered over the course of 12 weeks had a higher number of cocaine free urine tests during weeks 9–16 of the study than participants who received placebo injections or who produced a smaller antibody response to the vaccine [55]. These participants were also more likely to exhibit a 50% reduction in cocaine use between weeks 8–20 of the study relative to those who mounted a less robust immune response to the vaccine. However, a subsequent randomized, double-blind, placebo-controlled, Phase III clinical trial involving 300 cocaine-dependent participants in outpatient treatment

programs across six sites failed to demonstrate efficacy of the TA-CD vaccine [56]. Participants in this study received five vaccinations (400 mg each or placebo) over the course of 13 weeks, and 67% of the fully vaccinated participants displayed a robust antibody response (≥42 mg/ml). Vaccinated participants did not, however, have fewer cocaine-positive urine tests than participants receiving placebo injections, and participants with a robust antibody response did not exhibit a significant reduction in cocaine-positive urine tests relative to participants who mounted a lesser immune response. Participants who generated robust immune responses to the vaccine were, however, more likely to complete the study than those with weaker immune responses.

The second cocaine vaccine undergoing clinical trials is the dAd5GNE vaccine. One major drawback to the TA-CD vaccine was that it did not consistently elicit high titers of cocaine-specific antibodies. For example, in one study [55] only 38% of the vaccinated participants generated antibodies at the concentration projected to be required for efficacy. The dAd5GNE vaccine consists of the cocaine analog, GNE (6-(2R,3S)-3-(benzoyloxy)-8-methyl-8-azabicyclo [3.2.1] octane-2-carboxoamido-hexanoic acid) connected to disrupted adenovirus capsid proteins administered with Adjuplex (Advanced BioAdjuvants, LLC, Omaha, NB) adjuvant, and was designed to elicit a strong immune response from humans [57]. In rodents, this vaccine has been demonstrated to elicit high and persistent titers of cocaine-specific antibodies, attenuate the passage of cocaine from the peripheral circulation to the brain, reduce cocaine self-administration on a progressive-ratio schedule, and reduce cocaine-induced reinstatement of cocaine self-administration following extinction [57, 58]. The vaccine also produced high antibody titers in Rhesus macaques, reduced the penetration of cocaine to the CNS [59], and reduced reacquisition of cocaine self-administration following extinction [60]. The dAd5GNE vaccine is currently in a Phase I clinical trial, but results are not yet available.

Vaccines have also been developed against nicotine with the intention of helping users quit and remain abstinent. Vaccines that have been or are being examined in clinical trials include NicVax, Nic-002 (Nic-Qb), TA-NIC, Niccine, and SEL-068. None of these vaccines are currently approved for the treatment of tobacco use disorder, but further refinement and evaluation appears to be warranted. Because peer reviewed data related to many of these vaccines are limited, this discussion will focus on NicVax and Nic-002 (Nic-Qb). NicVax (3′-AmNic-rEPA) was one of the earliest candidate vaccines directed against nicotine. In preclinical studies, antibodies generated in response to this vaccine in rabbits and injected into rats reduced the passage of intravenously administered nicotine to the brain in a dose-dependent manner and attenuated the effects of nicotine on systolic blood pressure and locomotor activity [61]. Similarly, active immunization of rats elicited the production of nicotine-specific antibodies and also attenuated the passage of nicotine to the brain [61]. Active immunization also reduced nicotine self-administration in rats [62].

Single photon emission computed tomography (SPECT) data collected from nicotine-dependent human participants, indicates that active immunization with NicVax reduces the binding of nicotine to β2-nicotinic acetylcholine receptors in the brain [63], and the results of a study involving 68 current smokers assigned to receive four injections of vaccine (50, 100, or 200 mg) or placebo indicated that the vaccine was well tolerated and that the nicotine-specific antibodies were elicited in quantities believed to be sufficient for efficacy at the highest dose [64]. Participants receiving the highest dose of vaccine were also more likely to achieve 30 days of abstinence than participants receiving lower doses of the vaccine or placebo injections. The results of a subsequent Phase II clinical trial [65] in which 301 smokers were assigned to receive four or five doses of NicVax (200 or 400 mg/injection) or placebo over the course of 26 weeks indicated that participants who received five

400 mg doses of vaccine had higher prolonged abstinence rates through both 6 and 12 months relative to participants receiving placebo. In addition, participants with the highest antibody response (top 30% across all vaccine doses) were more likely to achieve eight weeks of abstinence between weeks 19–26 of the study, had higher rates of continuous abstinence from weeks 19–52 of the study, and had higher rates of 7-day point prevalence abstinence at weeks 26 and 52 of the study compared to participants receiving placebo. Participants in the high antibody response group were also more likely than participants receiving placebo to exhibit prolonged abstinence through 6 and 12-months. Unfortunately, while two subsequent Phase III clinical trials with NicVax confirmed that the vaccine was safe and well tolerated, six injections (400 mg each) of NicVax failed to significantly alter abstinence rates relative to placebo [66]. An additional Phase IIb study was conducted on the effectiveness of NicVax in combination with varenicline and motivational interviewing, however, this study too failed to establish a significant effect of NicVax on abstinence rates relative to participants receiving placebo [67].

Nic-002 (Nic-Qb), a vaccine consisting of a virus-like particle (VLP)-nicotine conjugate also showed both preclinical and clinical potential for reducing nicotine use. This vaccine yielded high titers of nicotine-specific antibodies in mice, rats, and rabbits, and vaccination of mice significantly reduced brain nicotine levels [68]. The report of the results from a European Phase I randomized, placebo controlled clinical trial in which 32 healthy human participants received two vaccinations separated by four weeks and 8 participants received control injections indicated that the vaccine was generally well-tolerated and produced a robust immune response with high affinity, nicotine-specific antibodies [68]. The results of a subsequent phase II study in which participants, were scheduled to receive five 100 mg vaccinations of Nic-002 with alum adjuvant (n = 229) over four months or alum alone as the placebo (n = 112) [69] indicated that, continuous abstinence rates from months 3 to 6 of the protocol, did not differ between the vaccination (30.1%) and placebo groups (26.1%), the 1/3 of participants with the highest antibody response had a significantly higher continuous abstinence rate from months 2 through 6 of the study (56.6.%) compared to participants receiving placebo (31.3%). Furthermore, this effect was maintained through month 12 of the study (41.5% vs. 21.3%). While researchers believed these results to be encouraging, Novartis announced that an interim analysis of data from a subsequent Phase II study indicated that the vaccine failed to improve continuous abstinence rates, likely due to insufficient antibody titers [70], and its development appears to have been halted.

Developing vaccines against opioid analgesics presents some unique challenges. One consideration is that unlike nicotine and cocaine the metabolites of many opioid drugs are active and can have physiological and psychological effects of their own. A second consideration is that if vaccines are to be used for the treatment of opioid use disorder, they should not bind to and inactivate opioids that are used to assist with treatment for the disorder or are used to prevent overdose. Finally, vaccines directed against one opioid analgesic will ideally not bind to other analgesics which may be needed for pain management. While no opioid vaccines have been tested in clinical trials, several candidate vaccines have emerged from preclinical investigations with promising results against heroin, oxycodone and fentanyl.

One example of a vaccine that appears promising for the treatment of heroin use consists of a heroin-tetanus toxoid (TT) combination [71]. Following administration heroin is rapidly metabolized to 6-acetyl morphine (6 AM) and subsequently to morphine, and these two metabolites act via mu-opioid receptors to generate heroin's antinociceptive and rewarding effects. Preclinical studies with this vaccine have demonstrated that it generates substantial antibody titers with high affinity for

6 AM and heroin and much lower affinity for morphine, oxycodone, and methadone in both mice and monkeys. Additional vaccines using haptens derived from morphine, have also been demonstrated to reduce the CNS-mediated behavioral effects of heroin [72].

Vaccines have also been developed that attenuate the behavioral and physiological effects of oxycodone and/or hydrocodone in rodents [72]. One of these vaccines, comprised of an oxycodone-based hapten conjugated to keyhole limpet hemocyanin (KLH), is notable, in part, for the specificity of its action [73]. Rats immunized with this vaccine generated antibodies with high affinity for oxycodone and, to a lesser extent oxymorphone, an active metabolite of oxycodone. Importantly cross-reactivity with naloxone and naltrexone was 1.2% or less and was undetectable for methadone and buprenorphine. Vaccination also reduces brain oxycodone levels by as much as 51% following intravenous administration of 0.5 mg/kg of oxycodone and significantly reduced the antinociceptive effects of oxycodone as indicated by performance on the hot-plate test. Furthermore, vaccination significantly reduced the acquisition of oxycodone self-administration and the number of infusions administered indicating a reduction in reinforcing effects of the drug.

Given the ongoing opioid crisis, a vaccine with clinical potential has also been developed against fentanyl [74]. This vaccine consists of a fentanyl-based hapten conjugated to either KLH or GMP-grade subunit KLH (sKLH). Vaccination elicited an immune response containing fentanyl-specific antibodies in mice and reduced the antinociceptive effects of fentanyl (0.05 mg/kg, s.c.) by 60% as assessed by the hotplate test. In addition, this vaccine elicited an immune response from rats and reduced the antinociceptive effects of fentanyl (0.05 mg/kg, s.c.) by 93% without significantly attenuating the antinociceptive effects of heroin or oxycodone. Fentanyl levels in the brain were also reduced by 30% following peripheral fentanyl administration (0.05 mg/kg, i.v.), and vaccination attenuated fentanyl-induced respiratory depression. Importantly, naloxone (0.1 mg/kg, s.c.) still reversed fentanyl-induced antinociception and respiratory depression following vaccination, indicating the vaccine does not render this important, life-saving drug ineffective.

While the results of clinical trials conducted thus far with vaccines against drugs of abuse have failed to yield consistent results indicating effectiveness, examination of the results obtained from participants who mounted a robust immune response has been encouraging. One hope is that advances in vaccine design improve will immune responses from participants [75]. Providing exogenous monoclonal antibodies against drugs of abuse to vaccinated participants might also provide a means of assuring that vaccine recipients have high antibody titers. This approach yielded improvements in combating the behavioral effects of nicotine in rats relative to vaccine administration alone [76]. It is also possible that modifying the route of administration could improve the efficacy of vaccines. For example, intranasal vaccine administration has been demonstrated to increase mucosal antibody levels against nicotine which could aid in the rapid immobilization of inhaled nicotine [77]. Intranasal administration of a cocaine vaccine has also recently been demonstrated to have advantages preventing cocaine-induced locomotion in mice [78].

Beyond simply attenuating the rewarding effects of drugs of abuse, vaccines may present additional advantages for SUD. Unlike available pharmacotherapies, the effects of vaccines can be long-lasting and require only periodic booster immunizations to maintain effectiveness. This may make vaccination more cost-effective than other treatments and preclude the need for daily adherence to drug regimens. Vaccines against drugs of abuse should also have a reasonably low behavioral/psychological side-effect profile as they do not have CNS effects of their own. Because of the lack of direct CNS effects, well designed vaccines should also not interfere with other

pharmacotherapies for substance use and could be combined with such therapies to enhance effectiveness. For example, while antagonist medications may be able to reduce the rewarding effects of drugs of abuse, users may increase their drug use in an attempt to override the blockade. This could leave the individual vulnerable to dangerous peripheral effects of the drugs. Vaccines may aid in combating these peripheral effects by limiting drug availability in the periphery as well. Co-administrations of vaccines against multiple drugs also has potential usefulness for individuals who abuse a mixture of substances such as fentanyl-laced heroin. The effectiveness of one such vaccine mixture (heroin/fentanyl) has recently been seen in mice [79].

Despite their promise, vaccines against drugs of abuse have several limitations. For example, vaccinated individuals could potentially increase substance intake to overwhelm the antibodies generated in response to the vaccine, and evidence of increased substance use by at least some participants has been reported in some of the studies discussed above [55, 56]. Additionally, participants with insufficient motivation to remain abstinent could discontinue treatment. Current skepticism about vaccines may also reduce the attractiveness of vaccines as an SUD treatment. Despite these limitations, with improvement, vaccination against drugs of abuse may still prove to be an efficacious tool to aid motivated individuals in recovery.

4. Transcranial magnetic stimulation and substance use disorders

Transcranial Magnetic Stimulation (TMS) is a noninvasive medical procedure involving the application of fluctuating magnetic pulses generated from a coil placed over the scalp that passes through the skull and into the brain generating electrical currents which alter neural activity by electromagnetic induction. The coil design can influence intensity, localization, and depth of stimulation. Multiple TMS pulses administered consecutively are referred to as repetitive or rTMS. Low frequency rTMS (LF-rTMS; ≤ 1 Hz) typically attenuates neural excitation and cortical excitability and higher frequency rTMS (HF-rTMS; 1–20 Hz) augments neural excitation, cortical excitability, and regional cerebral blood flow. Stimulation parameters, anatomical loci, and the current cortical activity also influence its facilitative or suppressive effects. rTMS results in strong moderately localized intracranial currents in the underlying cortex but also produces long lasting complex changes, neurotransmitter release, plasticity, and connectivity in distal neural circuitry [80–83]. The present form of TMS traces its origins to Barker and Colleagues who demonstrated the effects of magnetic stimulation on human motor cortex in 1985 [84]. The therapeutic efficacy of rTMS is currently under study for many psychological disorders and has U.S. Food and Drug Administration approval for the treatment of Major Depressive Disorder in adults [80].

The methods and mechanisms associated with rTMS-induced neuroplasticity and therapeutic efficacy for SUD are complex and reviewed elsewhere [80–83], however, the majority of studies have targeted the prefrontal cortex, more specifically the dorsolateral prefrontal cortex (DLPFC) [81–83]. This structure represents a desirable target not only for its accessibility but because it has been directly linked to neuroplastic changes associated with craving, impulsivity, and executive function all of which play central roles in addiction [80, 81]. Moreover, the DLPF is highly interconnected with other cortical and subcortical circuits associated with anhedonia, escalation of use, and relapse [82]. The potential of this approach has resulted in a significant number of studies in a relatively short period across a variety of addictive substances, brain loci, and employing a wide range of rTMS methods [81–83]. Most studies on the effects of rTMS for SUD have focused on

alcohol, cocaine, and nicotine and those literatures are highlighted below. Limited research has examined opiates, methamphetamine, and cannabis [85–87].

Multiple sham-controlled studies have been conducted to examine the efficacy of HF-rTMS on individuals with AUD with mixed results. One single-blind study examined rTMS (10 Hz) in 10 sessions to the right DLPFC and measured self-reported cravings at baseline following treatment and after 4 weeks. Significant decreases in craving were reported in patients who received rTMS versus sham rTMS [88]. A similar double-blind study comparing 10 sessions of right versus left DLPFC HF-rTMS (10 Hz) stimulation following treatment in those with AUD showed no difference in efficacy based on the side of treatment of administration but a significant reduction in craving scores in those administered rTMS [89]. Other studies using rTMS on the DLPC have failed to show effects of alcohol craving in those with AUD. A single session of rTMS versus sham treatment to the right DLPFC did not reduce craving immediately following treatment or when measured at home several days later [90]. Similarly, no significant differences in alcohol craving were reported after 10 days between sham rTMS and HF-rTMS of the left DLPFC, (20 Hz) [91]. Moreover, rTMS targeting the insula in alcohol-dependent participants in a double-blind, sham-controlled, randomized trial receiving 10 Hz rTMS or sham stimulation 5 days a week for 3 weeks showed no effects of rTMS on craving and alcohol consumption. A recent systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS; 11 studies) and rTMS (23 studies), most targeting aspects of the prefrontal cortex, on alcohol craving concluded there was no evidence of positive effects on alcohol craving [92]. However, the positive results found in some studies and the variability in study quality and methodology underscore the need for further research in this area [93].

To date no medication has clearly emerged as an efficacious treatment for cocaine or methamphetamine addiction [81], making the positive results with r-TMS for psychostimulant addiction particularly noteworthy. The benefits of a single 10 Hz rTMS exposure over right, but not left, DLPFC was found to transiently attenuate cocaine craving [94] and many studies have now illustrated the ability of multiple administrations to attenuate craving and use in cocaine dependent individuals. Among these is a between-subject randomized study examining stimulation of the left DLPFC using HF-rTMS (15 Hz administered during 8 sessions) versus a control group receiving a mixture of putative medications for cocaine addiction during a 29-day period. Results showed significantly more cocaine-free urine tests and lower craving scores in the rTMS treatment group [95]. In a study examining use, craving, and other markers indicative of cocaine dependence 20 individuals with cocaine use disorder (CUD) received 2 weeks of rTMS administration (15 Hz; 5 days/week, twice daily totaling 20 sessions) of the left DLPC, followed by 2 weeks of maintenance sessions (15 Hz, 1 day/week, twice a day). Of the 16 participants who completed rTMS treatment, 56% had negative urine tests, craving scores significantly decreased as did participants depressive symptoms, anhedonia, and anxiety [96]. Other studies have reported benefits of rTMS for CUD when applied to the medial prefrontal cortex [81] and rTMS induced reductions in methamphetamine craving [85]. As with other rTMS research, study protocols vary greatly when examining rTMS for psychostimulant craving and addiction, and it is of note that investigators are now attempting to synthesize knowledge gained across studies to design and optimize a rTMS protocols for treating CUD [97].

The significant degree of support for the efficacy of rTMS for SUD comes from research on nicotine dependence [83]. Multiple studies have reported 1–2 rTMS

sessions applied to the left DLPC results in reduced craving for cigarettes [83]. Repeated rTMS has also consistently yielded attenuated nicotine craving though the persistence of the effects remains unclear. For example, a randomized sham-controlled study administering 10 daily (10 Hz) rTMS to the left DLPC reduced cigarette consumption as measured by self-report and urine cotinine levels and cue-induced craving, though these effects dissipated with time [98]. The majority of studies of rTMS for SUD have focused on the efficacy of rTMS alone while some started to examine it in combination with other therapies. One study examined participants randomly assigned to receive 13 daily treatments of high-frequency, low-frequency or sham rTMS with and without cue exposure prior to treatment. Deep rTMS was bilaterally administered above the lateral prefrontal cortex and insula. High, but not low, frequency deep rTMS significantly attenuated cigarette smoking and when combined with smoking cues further facilitated reduction in cigarette use leading to an abstinence rate of 44% following the treatment and an estimated abstinence rate of 33% at 6 months [99]. A recent systematic review of the efficacy of rTMS for nicotine consumption and craving concluded that no recommendation beyond the possibility that HF-rTMS of the left DLPFC is effective for attenuating craving and consumption could be made and that while rTMS may be most effective when combined with other approaches, recent results obtained when combining approaches require replication and more rigorous evaluation [100].

Because rTMS is a neural circuit-based treatment approach rather than neurotransmitter focused and is directly administered to the brain, rather than systemically given, it is well tolerated. Adverse events are uncommon and tend to include transient headache and scalp discomfort. However, caution applying rTMS may be warranted in those with greater seizure risk such as individuals actively using psychostimulants or undergoing alcohol withdrawal [80]. rTMS may also be advantageous as it circumvents issues of medication adherence, cost, and side effects associated with most pharmacotherapies. The long-term efficacy of rTMS for decreasing drug craving in those with SUD is a potential concern given most studies assess these variables following relatively short-term administration periods (days-weeks) [81–83] or after limited follow-up periods [89]. However, one recent study suggests rTMS effects have the potential to be more protracted [85].

While initial rTMS results investigating craving and substance use among those with SUD are promising current findings still require replication in double blind studies with larger sample sizes [81–83]. Moreover, studies showing reduction in symptoms of SUD beyond craving are uncommon [82] and given long-term effects from rTMS are only achieved following weeks of stimulation sessions the approach may be time intensive and costly [86]. Several aspects of rTMS treatment are robust and reliable such as regional specificity, depth of magnetic field, dose dependent amplification of behavior, polysynaptic engagement, and frequency dependent effects. However, many treatment parameters are yet to be determined including the optimal number of daily sessions, the optimal number of total sessions, efficacy of rTMS for attenuating drug consumption when applied to regions other than the DLPFC, optimal coil orientation relative to anatomy, and an appreciation of the synergy between rTMS and other therapeutic approaches [80–82]. It is also worth highlighting that much of our understanding of addiction has moved away from purely drug-centered model which focuses on the neurochemical changes that result from drug exposure towards a more individual-centered model whereby individual differences in vulnerability to developing addiction are recognized. With this paradigm shift future application of rTMS might benefit from using individual MRIs and TMS navigator devices to individualize and maximize its physiological and therapeutic effects [82, 93].

5. Conclusion

The process of bringing a new therapeutic approach into practice in a larger population is multifaceted and hinges on regulatory procedures, safety, efficacy, need, cost, among other variables. Moreover, this process is rarely linear as new research is published and the zeitgeist for various therapies changes. Where there remains little controversy is that while SUD treatment has seen growing success, evidenced-based therapeutic options are still limited and not effective for all patients. Developing novel approaches continues to be paramount given the psychological, social, healthcare, and economic costs of drug addiction.

The reemergence of research on serotonergic hallucinogens, most notably psilocybin, is of particular significance as it appears effective and well tolerated for treating SUD in the limited research that has been conducted. This conclusion is further bolstered by research examining the efficacy of psilocybin and related drugs for the variety of psychological disorders that are also part of the milieu of addiction. The dramatic and long-lasting nature of psilocybin's effects on meaning, spirituality and drug use appears to address the chronic nature of SUD in ways not achieved by most treatment approaches. Likewise, the potential therapeutic use of rTMS for SUD and other psychological disorders is notable for its efficacy, safety, and anti-craving effects, the latter of which is both central to addiction yet remains particularly challenging to resolve. The promise of these two approaches is hard to overstate yet in the absence of findings from larger randomized, double-blind clinical trials these approaches will continue to be viewed as merely promising. Anti-addiction vaccines, while potentially beneficial, require further technical refinement and appreciation of their place among therapeutic modalities.

As research on these approaches progresses it is not too early to consider how these therapies might be scaled to treat the large number of people affected by SUD. While some of these questions have begun to be addressed, such as the optimization of treatment protocols and how to best integrate them with other treatment modalities, larger issues loom. Who will be trained to administer these therapies and where will they be administered? Overcoming the public's negative perception and misunderstanding of hallucinogenic drugs, electroshock therapy, and vaccine hesitancy are all barriers to scaling these therapeutic approaches which are unfamiliar to most and therefore susceptible to misunderstanding and misinformation. The use of newer pharmacotherapies for SUD over the past 30 years has been slow to be adopted by healthcare providers partially due to their lack of awareness and comfort with these new approaches. The inclusion of these interventions in graduate education across medical, psychological, and healthcare occupations might promote their integration as future treatment options for those with SUD. Consideration of these issues today will likely ease the transition of these and other novel therapeutic techniques for SUD into widespread use moving forward.

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