Studying the Effects of Classic Hallucinogens in the Treatment of Alcoholism: Rationale, Methodology, and Current Research with Psilocybin

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Abstract: Recent developments in the study of classic hallucinogens, combined with a re-appraisal of the older literature, have led to a renewal of interest in possible therapeutic applications for these drugs, notably their application in the treatment of addictions. This article will first provide a brief review of the research literature providing direct and indirect support for the possible therapeutic effects of classic hallucinogens such as psilocybin and lysergic acid diethylamide (LSD) in the treatment of addictions. Having provided a rationale for clinical investigation in this area, we discuss design issues in clinical trials using classic hallucinogens, some of which are unique to this class of drug. We then discuss the current status of this field of research and design considerations in future randomized trials.

Keywords: Addiction, alcohol dependence, alcoholism, clinical trials, drug abuse, hallucinogens, psilocybin, psychedelic drugs.

1. RATIONALE FOR THE STUDYING THE USE OF CLASSIC HALLUCINOGENS TO TREAT ALCOHOL DEPENDENCE

"Classic hallucinogens" are defined for purposes of this review as those agents that have effects similar to those of mescaline, psilocybin, and LSD, exert their effects primarily by activating serotonin (5-HT) 2A receptors [1]. A number of articles and chapters have reviewed the literature on the use of hallucinogens in the treatment of addictions [2-6], with the recent addition of two reviews that incorporate current research on the effects of classic hallucinogens more generally and discuss possible mechanisms of action [7-8]. Here we provide a brief summary of the most important lines of evidence.

1.1. Relevant Preclinical Research

Although classic hallucinogens bind to many serotonin receptor subtypes and other receptors including D1 and D3 receptors [9], the psychoactive effects of all classic hallucinogens appear to depend primarily on their actions at 5HT2A receptors [1, 10]. Ketanserin, a 5HT2A antagonist, blocks most of the subjective effects of psilocybin in humans [11]. Stimulation of 5HT2A receptors by 5HT2A agonists causes activation of sub-populations of pyramidal cells in cerebral cortex by enhancing glutamatergic neurotransmission within intracortical networks, particularly those involving cortical layer V [12-15]. In mouse models, effects of hallucinogenic 5HT2A agonists are mediated by different intracellular signaling cascades from those activated by serotonin and non-hallucinogenic 5HT2A agonists [16-18]. The effects of LSD are mediated in part by pathways involving pertussis toxin-sensitive Gi/o proteins and Src, while the effects of lisuride (a non-hallucinogenic 5HT2A agonist) do not depend on these pathways [16]. Moreno and colleagues demonstrated that the metabotropic glutamate mGlu2 receptor, which forms complexes with 5HT2A receptors, is necessary for the pharmacological and behavioral effects of hallucinogenic 5-HT2A agonists [19].

Very little is known about persisting brain changes related to use of classic hallucinogens in treatment of addiction, but there are animal data suggesting directions for future research. Administration of classic hallucinogens in rat models has been shown to induce down-regulation of 5HT2A receptors, particularly those in the anterior cingulate and frontomedial cortex, likely accounting for the rapid development and reversal of behavioral tolerance to most classic hallucinogens [20-21]. This is interesting in relation to evidence that 5HT2A receptors are upregulated with chronic alcohol exposure [22]. DOI and serotonin increase expression of glial cell line-derived neurotrophic factor (GDNF) mRNA in glioiblastoma cells by a 5HT2A-dependent mechanism [23]. Through its action on 5HT2A receptors, DOI has also been shown to increase levels of mRNA for brain-derived neurotrophic factor (BDNF) in rat parietal cortex and other neocortical regions, with decreases in the hippocampus and no change in piriform cortex [24]. These findings are relevant because levels of BDNF and GDNF are inversely related to alcohol consumption and conditioned place preference in animal models [25]. DOI activates intracellular signaling cascades associated with dendritic spine remodeling on rat pyramidal cells, and transiently increases the size of dendritic spines on cortical neurons [26]. At present there is no direct evidence as to whether any of these mechanisms mediates antiaddictive effects of classic hallucinogens.

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1.2. Neuroimaging Studies of Acute Effects of Classic Hallucinogens on Functioning of the Human Brain

PET, SPECT, and fMRI technologies have been applied to studies of the acute effects of classic hallucinogens, specifically psilocybin and ayahuasca (an herbal decoction containing dimethyltryptamine (DMT) and beta-carbolines including harmine, harmaline, and tetrahydroharmine. The beta-carbolines are monoamine oxidase inhibitors that render DMT orally active, as well as having psychoactive effects themselves). In a PET study of effects of psilocybin (15-20 mg PO), Vollenweider and colleagues found that global cerebral glucose metabolism increased by 19.9% relative to baseline, with the largest increases in thalamus and frontomedial, frontolateral, anterior cingulate, and temporomedial cortices [27]. In a placebo-controlled study by the same group, psilocybin 0.2 mg/kg produced increased glucose metabolism in the right anterior cingulate and right frontal operculum, with decreased metabolism in the right thalamus and left precentral cortex [28]. A placebo-controlled SPECT study of ayahuasca administration by Riba and colleagues demonstrated increased blood flow in the anterior insula bilaterally, in right anterior cingulate/frontomedial cortex, and in the left amygdala/parahippocampal gyrus [29]. In contrast, a recent fMRI study from Carhart-Harris and colleagues, using psilocybin 2mg administered intravenously, found that psilocybin administration was associated with decreases in regional cerebral blood flow and BOLD signal, with strongest effects in anterior cingulate cortex/medial prefrontal cortex, posterior cingulate cortex, and thalamus [30]. Psilocybin also decreased functional coupling between medial prefrontal cortex and posterior cingulate cortex. Another report from this group demonstrated that intravenous psilocybin increased activation in multiple brain regions in response to recollection of autobiographical events [31]. Clearly we are only beginning to understand the acute effects of classic hallucinogens on brain function. In addition, there have been no neuroimaging studies of the persisting effects of classic hallucinogens. Since effects of some sort must persist beyond the period of acute intoxication for the treatment to have any clinical value, persisting brain effects are more directly relevant to therapeutic benefit than are acute brain effects.

1.3. Can Administration of Classic Hallucinogens Precipitate or Facilitate Lasting Psychological Change?

Classic hallucinogens (primarily LSD) were studied extensively from the 1950s through the early 1970s in the treatment of alcohol and drug addiction as well as anxiety, depression, obsessive-compulsive disorder, and other conditions. Two contrasting models of treatment developed: the psycholytic and psychedelic models [6, 32]. In psycholytic therapy, low to moderate doses of hallucinogens were administered, usually on many occasions over a period of months to years, to facilitate therapy based on traditional psychoanalytic principles [33-34]. The psychedelic method used higher doses of LSD, administered once or on a few occasions, with the goal of inducing a "peak-psychedelic" (mystical) experience [35-36]. The psychedelic model held that such experiences often produced lasting change in habitual patterns of thought, emotional response, and behavior. Many of the studies from the 1960s, particularly those employing the psychedelic model, reported changes on measures of personality following hallucinogen administration [37-41].

More recently, rigorous quantitative studies have demonstrated that psilocybin can occasion profoundly meaningful experiences that have significant lasting effects in normal volunteers [42-45]. In a double-blind study by Griffiths and colleagues, 22 out of 36 participants receiving a single high-dose psilocybin session met a priori criteria for a "complete mystical experience" [44]. Fourteen months after the psilocybin session, 67% of participants rated it as one of the 5 most significant spiritual experiences of their lives, and 61% reported that the experience was associated with "moderate to extreme positive behavioral change," as well as positive changes in attitudes, mood, and altruism [43]. These self-reports correlated with ratings by community observers who reported similar positive changes in participants. In a second study in which participants received a range of doses of psilocybin, 72% of volunteers reported a mystical experience at one of the highest two doses [45]. Persisting positive effects one month after the psilocybin session were found to be dose-related. In another recent human administration study by a different group of investigators, the hallucinogen MDA was also reported to induce mystical experiences [46].

1.4. Relationship of Sacramental Hallucinogen Use to Use of Other Substances

Cross-sectional studies have consistently shown decreased rates of alcohol dependence among members of religions that use serotonergic hallucinogens as a regular part of their practice, including the Native American Church, which uses the mescaline-containing peyote cactus as a sacrament [47], and both Brazilian [48-49] and US [50] sects using ayahuasca. Although cultural norms within these religions likely contribute to such effects, the pattern suggests the possibility of a pharmacological effect as well.

1.5. Past Research on Classic Hallucinogens for Alcohol and Drug Dependence

In the 1950s through early 1970s there was extensive research on the use of the prototypical classic hallucinogen LSD in the treatment of alcoholism (For reviews see [2-6]), with more limited research on LSD for the treatment of drug addiction [51-52] and dipropyltryptamine (DPT) for alcohol dependence [53-54]. At least a dozen trials included some form of control group [55-56]. A recent meta-analysis [55] examined 6 randomized trials (5 of which were fully double-blind) of LSD for alcohol dependence [57-62]. A total of 325 participants received active treatment with LSD and 211 received control treatment. These studies all employed a single high-dose LSD session, and the vast majority of participants were male inpatient alcoholics. The studies were otherwise quite heterogeneous, with sample sizes varying from 20 to 176, LSD doses ranging from about 210 to 800 mcg, control conditions including placebo, low dose (50 mcg) LSD, ephedrine, and amphetamine, and great variability in preparation and debriefing of subjects and in the conditions during the LSD sessions. At the first post-

treatment follow-up (ranging from 1 month to 12 months) the odds ratio for improvement was 1.96 (95% confidence interval 1.36-2.84, Z = 3.59, p = .0003). Among the 5 studies reporting dichotomous outcomes, 59% of the LSD-treated participants were significantly improved, *vs* 38% of the control participants (pooled benefit difference 16%, 95% confidence interval 8%-25%, p = .0003, number needed to treat = 6). Treatment effects decreased with the duration of follow-up, but remained significant at 6 months. These effects were highly consistent across the 6 studies. These robust effects provide a strong rationale for resuming clinical investigation of classic hallucinogens for the treatment of alcoholism and other addictions.

1.6. Recent Studies of Psilocybin as Treatment for Various Conditions

The past decade has seen a resurgence of interest in potential clinical applications of classic hallucinogens, particularly psilocybin. The effect of varying doses of psilocybin (doses up to 0.3 mg/kg PO) on symptoms of obsessive compulsive disorder was tested in 9 subjects in a within-subjects design [63]. All doses tested produced significant decreases in OCD symptomatology, but there was no effect of dose or dose-by-time interaction. Using a double-blind, cross-over design, Grob and colleagues administered psilocybin 0.2 mg/kg *vs* placebo to 12 patients with anxiety related to advanced cancer [64]. Although significant treatment effects were not demonstrated in this pilot study, there were statistical trends suggesting a positive effect of psilocybin on mood. The relatively low dose of psilocybin may have limited efficacy in this study. Additional clinical trials are currently under way in cancer patients at Johns Hopkins University (NCT00465595) and NYU (NCT00957359). Currently, psilocybin is being investigated as an adjunct in smoking cessation treatment in an open label pilot study at Johns Hopkins University [65] and for alcohol dependence at the University of New Mexico (NCT01534494). Studies have also been proposed for the treatment of depression [10, 31].

2. METHODOLOGICAL ISSUES IN CLINICAL TRIALS USING HALLUCINOGENS

Hallucinogens used in clinical contexts have several features that, taken together, create some unique issues relating to the design of clinical interventions and research protocols to test their efficacy and effectiveness. Hallucinogens have pronounced acute psychoactive effects (as do some other drugs such as opioids, sedatives, and stimulants). They are also hypothesized to have persisting effects that outlast the acute pharmacologic effects, i.e., long after the drug is gone (like vaccines and non-pharmacologic somatic treatments such as ECT and TMS). The persisting effects may be mediated by the acute psychological effects. Although there are obviously brain correlates of these effects, it cannot be assumed that the therapeutic brain changes could be obtained without the subjective experience. No medications share this property, but psychotherapies do. The effects of hallucinogens vary markedly from individual to individual and from session to session, depending on the context, expectations, and environment of the session. In many cases their clinically relevant effects are hypothesized to be dependent on the therapeutic context, so that what is really being measured is the combined effect of the drug-psychosocial treatment combination.

2.1. Choice of Drug

Although a good case can be made for studying the use of ibogaine derivates [66-72] and NMDA antagonists (e.g., ketamine) [10, 73-76] to treat addiction, the focus of the current review is classic hallucinogens. Within this class, based on experience to date the two leading candidates for application in the treatment of addiction are LSD and psilocybin. Both drugs have used extensively in human research and clinical practice. LSD has the advantage of an extensive prior literature of alcoholism treatment trials. Psilocybin has some other advantages. Recent human studies with psilocybin confirm the relatively benign safety profile [44, 63-64, 77-79]. Its duration of action (approximately 6 hours) is intermediate between that of LSD or mescaline and that of DMT. This duration makes it practical to administer on an outpatient basis during a session lasting no more than 8 hours, but, unlike DMT, allows ample time for the experience to be integrated into normal consciousness. Unlike DMT and DPT, it can be administered orally.

2.2. Number of Sessions and Dose

The dose used and the number of sessions depends on the intended effect and the model of treatment being used. In the addiction treatment field, most studies have used the psychedelic model with relatively high doses of LSD and one or very few sessions. It was believed that having a "peak-psychedelic" or mystical experience was the most important predictor of positive effect. The controlled trials for alcohol dependence all used high doses ranging from 3mcg/kg (roughly 210 mcg) to 800 mcg (roughly 11.4 mcg/kg), with no evidence of a dose-response relationship within this range [55]. There are no published studies using psilocybin in the treatment of addiction, so the dose range must be estimated from other contexts. Based on experience, Fisher reported that a standard psychedelic dose of LSD was 300-500 mcg, and for psilocybin 20-40 mg [80]. In their studies with psilocybin in normal volunteers, the Johns Hopkins group has reported the effects of a range of psilocybin doses of up to 30 mg/70 kg (0.43 mg/kg) [44, 79, 81-83]. Persisting positive effects increase monotonically as a function of dose, but acute adverse effects increase as well, with severe anxiety and transient paranoia being much more common at 30 mg/70 kg than at 20 mg/70 kg (0.29 mg/kg) [79]. Seventy-two % of participants reported a "complete mystical experience" at either the 20mg/70kg or the 30mg/kg dose. Adverse effects were less common and severe when doses were given in escalating order. Persisting adverse effects have not been observed at any dose. Investigators in the 1950s and 1960s reported that alcohol dependent patients appeared to be relatively resistant to the effects of LSD, and to require higher doses than most other patients [84-86] (patients with obsessive compulsive disorder are another group purported to have low response to LSD [32]). However, there have not been any quantitative comparisons of dose/response in different clinical populations. Based on these data, the dose range of approximately 3-6 mcg/kg of

LSD or 0.29-0.43 mg/70 kg of psilocybin seems to be an appropriate starting point for addiction treatment studies.

Although the randomized trials of LSD for alcohol dependence used a single high-dose session with the goal of inducing a "single overwhelming experience," other variations of the psychedelic model were also used. Some investigators used multiple sessions, sometimes starting with lower doses and making dose adjustments as needed to optimize the effect. Some LSD studies also used "booster" doses after 1-2 hours if the initial dose did not appear to have an adequate effect [87-89]. Some practitioners and researchers also combined classic hallucinogens with psychostimulants in the belief that this would enhance the effects, added benzodiazepines to prevent or treat anxiety, and/or administered barbiturates or antipsychotics to terminate the session or induce sleep [36, 80, 90].

In sum, based on existing data, there is strongest support for the high-dose, single-session model. However, given the suggestion that there may be an relatively narrow window within which the desired intensity of effect is achieved while minimizing adverse effects, the evidence that adverse effects can be minimized by escalating doses rather than starting with a maximal dose, and the apparent attenuation of effects over time, a case can be made for a model that includes a few (2-4) sessions with the dose escalating until an optimal effect is achieved and/or dose-limiting side effects are experienced. Other models are possible but lack empirical support. For example, it would be possible to mimic the pattern of use in psycholytic therapy and religious contexts, i.e., smaller doses taken at regular intervals (e.g., once every two to four weeks) over a longer period of time, possibly administered in group sessions. There are no clinical trial data on the use of such an approach for the treatment of addictions.

2.3. Psychosocial Treatment

In any psychopharmacotherapy trial it is desirable to standardize psychosocial treatment, even if this treatment consists only of "pharmacologic management" by the treating clinician. Ideally treatment is standardized through use of a manual, with uniform procedures for training, supervision, and fidelity monitoring. For most pharmacotherapy trials, psychosocial treatment can be thought of as a "platform" upon which contrasts of interest (e.g., active medication *vs* placebo) can be tested. In many cases the psychosocial treatment is intentionally kept at a low level of intensity to minimize placebo response, and treatment may be focused on medication adherence to maximize treatment exposure.

Studies involving therapeutic applications of classic hallucinogens differ from most other trials in that the pharmacologic treatment and the psychosocial elements of treatment are best considered as an integrated package. We do not necessarily expect that these drugs will have any beneficial effects in the absence of an appropriate set and setting. The psychosocial treatment is, at minimum, required to provide a "container" within which the drug can be administered and the effects can be experienced safely. The psychosocial treatment might or might not also help establish the purpose or therapeutic goals of the session, provide a conceptual framework for the experience, promote particular kinds of drug experiences (in terms of specific content, general focus, or tone), provide directive or non-directive therapy during the drug experience, promote the integration of the experience in the interest of therapeutic change, and/or provide additional therapeutic elements not directly related to the drug administration.

Different models of treatment with hallucinogens have differed in their hypotheses for the mechanism of action, and have employed differing therapeutic approaches. As discussed above, psycholytic therapeutic approaches are based primarily in the psychoanalytic model, and use LSD or other hallucinogens as a means to accelerate the process of psychodynamic psychotherapy [33]. Psycholytic therapy typically involves active verbal psychotherapy while the patient is experiencing the effects of the hallucinogen. Psychedelic therapy, on the other hand, is based on the premise that hallucinogens produce pronounced change primarily by facilitating a "peak-psychedelic" or mystical experience, and the therapy (as well as the relatively high doses of drugs used) is geared toward maximizing the probability of such experiences [36, 61]. However, psychedelic psychotherapists caution against active attempts to guide the patient toward having particular types of experience, rather encouraging the patient to let go and accept whatever experience they have during the session [54, 61]. During the session, psychedelic psychotherapists are generally non-directive and do not attempt to conduct verbal psychotherapy, instead usually providing music for the patient to listen to [91].

Regardless of the model, it seems prudent to recommend that the psychosocial treatment provide sufficient support to promote trust and rapport and minimize the probability of traumatic drug experiences, and that it include sufficient monitoring and evaluation to identify any significant adverse events and intervene as needed. Johnson and colleagues have published guidelines for maximizing safety in the administration of classic hallucinogens [92]. Beyond the safety issues, in clinical applications the psychosocial treatment should be compatible with the hypothesized mechanisms of drug action, and ideally designed to work synergistically with the pharmacologic treatment to produce the effects that are thought to promote therapeutic change. Many empirically validated forms of psychosocial treatment for addictions appear to be adaptable for use in the context of hallucinogen assisted treatment, including cognitive behavioral approaches [93], 12-step facilitation [94-96], Motivational Interviewing/Motivational Enhancement Therapy [97], and family/couples therapies [98-99].

As in clinical trials employing a psychosocial treatment, therapists providing psychosocial treatment in the context of treatment with classic hallucinogens should be trained to fidelity, and supervised and monitored appropriately. They need to have sufficient knowledge and experience of the possible range of responses to the drug and to be equipped to handle any situations that may arise. Historically some authors have argued that it is critical for the therapist to have personal experience with the effects of hallucinogens in order to be able to appreciate what the participants are experiencing and to be effectively supportive [100-101]. However, this hypothesis has not been tested empirically.

Personal experience can enhance understanding, but can also serve as an obstacle since the therapist may tend to assume similarities between the participant's experience and the therapists experience, which similarities may not in fact exist. At present, none of the groups actively conducting research involving hallucinogen administration to humans require that their therapists have personal experience with hallucinogens (historical or as part of training).

Consistent with the "set and setting" of Leary and colleagues [102], it is generally believed that the mental state of the participant (including expectancies and intentions in approaching a drug administration session) and the setting of the session will affect both the acute and the post-session effects of the session [92]. These issues have not been studied experimentally to any significant extent, although a recent report identified several individual state and trait variables that affected subjective responses to psilocybin [103]. Regarding persistent effects, it seems reasonable to suppose that a patient is more likely to experience therapeutic benefit if her intention in taking the drug is therapeutic (rather than satisfying curiosity or getting high). One would not necessarily expect therapeutic effects in drinkers who are not interested in changing their drinking. Again there are no data to support this supposition directly. However, if one hypothesizes that expectancies and intentions may be important predictors of outcome, this has implications for study design. Positive expectancies can be systematically encouraged in the psychosocial therapy. Positive intentions can be maximized through the use of careful patient selection and also the use of psychosocial treatment designed to heighten motivation, e.g., motivational interviewing [104].

2.4. Patient Characteristics, Potential Moderators and Sample Size

Careful patient selection is important to minimize the probability of adverse events in studies involving administration of hallucinogens [92]. In particular, personal or family history of psychosis is considered a contraindication because classic hallucinogens can precipitate psychosis, although this is rare in clinical research contexts [78, 92, 105]. Past exposure to psychedelics should be considered, as participants with an extensive history of psychedelic use could have a less pronounced response to one or a few sessions. For outpatient studies, adequate psychosocial stability and meaningful relationships are important to ensure that participants have adequate support following the drug administration sessions. More generic considerations for participant inclusion include lack of medical contraindications, adequate current severity to detect improvement, relative homogeneity in terms of severity, co-occurring psychiatric disorders, and other substance use disorders, and reasonable likelihood of completing the treatment and follow-ups.

For patients included in a trial, careful attention should be given to any characteristics that are hypothesized to affect response to the psychedelic drug treatment. Alcoholism typology affects response to other serotonergic medications [106-109], so this should be considered, and, at a minimum, age of onset should be assessed. Other characteristics related to addiction that could affect treatment response include severity, craving, and other comorbid substance use. Since the vast majority of participants in past trials of classic hallucinogens for alcohol dependence have been men, we have no information on the effects of these agents on men *vs* women. Personality and psychopathology (including mood and anxiety symptoms) are possible moderators of treatment effect. In relatively large studies, genetic analysis may be useful to identify genotypes that predict better or worse response to treatment with classic hallucinogens. Significant interactions of genotype and treatment have been observed for both naltrexone [110] and ondansetron [111].

Sample size of definitive efficacy trials should be large enough to detect clinically meaningful effects with adequate power. The history of LSD treatment for alcoholism amply demonstrates the risks of inadequate size, as the treatment was concluded to be ineffective on the basis of multiple underpowered studies that did not achieve statistical significance. Example optimistically, given the simplest possible 2-group, single-hypothesis design, and an effect size comparable to those observed in the 5 LSD trials reporting dichotomous outcomes in Krebs and Johansen meta-analysis [55], over 150 participants per group would be required to achieve 80% power. In a more typical example of a phase 3 trial, the pivotal trial of depot naltrexone (Vivitrol®), the most recent drug approved for alcohol dependence, included 624 participants allocated to three groups (380 mg, 190 mg, and placebo) [112]. The effect on the primary outcome, percent heavy drinking days, was just large enough to be statistically significant (hazard ratio = 0.75, 95% confidence interval 0.60-0.94, p = .03).

2.5. Outcome Measures and Mediators

There are no generally accepted criteria for success in addiction treatment research. In alcoholism research, although long-term total abstinence is the most desirable outcome, dimensional measures such as percent days abstinent, percent heavy drinking days, and drinks per drinking day have been used in many recent large-scale trials [112-114]. Dimensional measures that include abstinence are time to first drink, time to relapse, and longest duration of abstinence. Self-report measures are subject to bias but have generally been found to be reliable and valid in alcoholism studies [115]. Collateral informants may be used to confirm or falsify self-report. Objective biological measures of recent alcohol use such as GGT, carbohydrate-deficient transferrin, ethylglucuronide, and phosphatidyl ethanol, obtained from samples of blood, urine, or hair, are currently too expensive or unreliable for use as primary outcome measure in most contexts, but they hold promise as the technology continues to improve [116]. In drug addiction treatment studies, self-report has been shown to be reliable and valid in many cases, but there has been a significant number of studies in which self report deviated substantially from objective measures [117-118]. Objective biological measures such as urine drug screens are often used as primary outcomes or combined with self-report to form composite measures, which perform better under some circumstances than either considered separately [118]. Categorical measures of clinical outcome can be constructed from continuous outcome data in number of ways, e.g., "good clinical outcome" used in the NIAAA COMBINE trial [114].

Addiction affects many life domains, and treatment can affect outcomes in these areas. Broader functional measures include consequences of substance use, quality of life measures, and psychological and medical health. Measuring outcomes in these domains is desirable in any addiction treatment study [119], and such measures were included in many of the psychedelic treatment studies of the 1960s.

Based on theoretical considerations and existing data, there are several domains that are particularly important to consider as proximal outcomes and possible mediators of effects on substance use in studies using classic hallucinogens to treat addictions. Most proximal to drug administration is the character of the drug experience. Dimensions of the experience and overall intensity can be reliably measured by instruments such as the Five-Dimensional Altered States of Consciousness questionnaire (5D-ASC) [120] and the Hallucinogen Rating Scale HRS [121]. The mystical quality of the experience has been shown in recent studies to be a significant predictor of beneficial change in normal volunteers [81-82]. Secondary effects of potential importance to addiction outcomes include enduring changes in mood and affect, anxiety, drug/alcohol craving, motivation, self-efficacy, personality, and values [8].

Neurobiological changes have not been assessed in prior studies of treatment of addictions with classic hallucinogens. There is an extensive and growing literature on acute effects classic hallucinogen effects including positron emission tomography (PET) [27-28, 122], single-photon emission computed tomography (SPECT) [29], functional magnetic resonance imaging (fMRI) [30-31], and other human laboratory studies [11, 77, 121, 123-148]. Although these studies are valuable for the information they provide about the brain activity associated with altered states of consciousness and how these acute changes in activity might affect outcome, neurobiological effects that persist beyond the period of intoxication would be more directly relevant to any persistent therapeutic effects on behavior and mental state. Such studies of persisting brain effects should be a priority for inclusion in future therapeutic trials of classic hallucinogens. In addiction treatment contexts, fMRI studies examining activation and functional connectivity during cue response, inhibitory control, and response to stress would be useful to test for effects that have been found for other medications [149-153] and psychotherapies [154-155]. PET and SPECT provide a mechanism for examining receptor density and receptor occupancy, as well as direct assessment of metabolism, which can only be inferred using fMRI. These technologies have been used to study the biology of addiction [156-160], but have not been used extensively to study treatment effects. Magnetoencephalography (MEG) can be used to measure brain activity directly on a shorter time scale than fMRI. This technology has been used extensively to study brain function in schizophrenia [161], neurodegenerative disorders [162], autism [163], and affective disorders [162], but has not been used to study acute hallucinogen effects, and has seen very little use in the study of addictions.

2.6. Design

2.6.1. Dealing with Interactions Between Pharmacotherapy and Psychosocial Treatment

The therapeutic intervention in a clinical trial of a classic hallucinogen is the combination of drug and psychosocial treatment. It is expected that there will be an interaction between the psychosocial treatment and the drug effect (drug/set/setting hypothesis). Stanislav Grof went so far as to maintain that there was no inherent tendency for a psychedelic drug to have harmful or therapeutic effects: the entire effect was due to the interaction of the non-specific drug effect, intrapsychic factors on the part of the patient, and the social envelope [32]. Although interactions may be paramount, factoral designs involving multiple psychosocial treatment conditions (e.g. 2*2 or more complicated) greatly increase the cost of a study, and there are serious ethical problems with administering hallucinogens without extensive preparation and support. Therefore, one simple and attractive design is to contrast the effect of a psychosocial treatment (alone or in combination with placebo or an active but putatively ineffective control medication) with that of the same psychosocial treatment combined with drug administration. The advantages to this design are that blinding is possible (although see considerations below), and it formally isolates the drug effect so that any difference between the groups can be attributed to the drug. However, a disadvantage is that in such a design is that the psychosocial treatment may have a different effect in the two groups as well, and there is no way to control for this. A significant portion of the psychosocial treatment must be devoted to preparing the participant for a psychedelic/mystical experience, which will occur rarely if at all in the control condition. That portion of the psychosocial treatment may be less helpful for patients not receiving active medication. In fact it could be countertherapeutic by engendering disappointment in participants who do not have an impressive experience. For these reasons, it is important to design the psychosocial treatment in such a study to be credible and potentially effective for patients who do not receive active medication, and to take pains to minimize demoralization in patients who do not have a strong experience from the medication. The pharmacotherapy may be thought of as adjunctive to a psychosocial treatment that is valuable in its own right.

An alternative is to contrast the effects of a classic hallucinogen combined with a psychosocial treatment designed to work with the drug with the effects of a different psychosocial treatment and/or medication of known efficacy. This design does not allow blinding or any inference to be made about the incremental effect of the drug itself, but does allow the effectiveness of the drug-therapy package to be compared to that of another well-defined approach. This is a critical clinical question, but one that is probably better asked only if the more basic question of efficacy has been answered affirmatively in double-blind trials.

2.6.2. Control Conditions and the Issues of Blinding

Maintaining double-blind conditions is challenging in studies involving psychoactive doses of hallucinogens due to

the pronounced subjective and objective effects of the drug. The effects themselves are not the problem, since they are inherent in the use these drugs and may indeed mediate therapeutic effects. The problem is that expectancies associated with the knowledge of receiving active medication may contribute to the observed effects of the active medication, and any effects of expectancies associated with knowledge of not receiving active medication (demoralization, poor outcome due to disappointment or belief that the active medication was not received) will contribute to the observed effects of the placebo. These effects may be magnified to the extent that the participant expects the drug to have powerful effects. For this reason among others, investigators should guard against suggesting to participants that only a particular type of experience (e.g., a mystical experience) is desirable and therapeutic. Still it is possible that many people volunteering for a hallucinogen treatment study will harbor hopes for an overwhelming experience that will cause a major change, and may be disappointed by a milder experience. Similarly, therapist behavior could be affected by observation of a participant having a strong emotional reaction or other pronounced effects during a session. For this reason, fidelity monitoring of behavioral interventions is particularly important is studies involving classic hallucinogens.

Use of placebo control in studies with hallucinogenic drugs has the drawback that patients will in most cases know whether they received active medication or not. Use of an active control such as a stimulant is an alternative method which was used in two of the double-blind controlled trials of LSD for the treatment of alcoholism [57-58]. Griffiths and colleagues used a high dose of methylphenidate as a control condition in a double-blind study of psilocybin effects in normal volunteers [44], with a complex blinding strategy described below. They reported in that study that 23% of sessions were misclassified by one or both of the session monitors, and that participants occasionally reported highly meaningful and personally significant experiences with methylphenidate. Another possibility is to use a low dose of the drug under investigation. Ideally this would be a dose that is noticeably psychoactive but low enough to be ineffective. This approach also was used in controlled trials of LSD treatment of alcoholism [60-61]. However, it is difficult to exclude the possibility that a low psychoactive dose could have therapeutic effects, complicating the interpretation of a null finding (for example, see [63]). Alternatively, an even lower dose could be used which is not measurably psychoactive and very unlikely to have therapeutic effects. An advantage of this approach over use of a true placebo is that participants could be truthfully told that they will receive some dose of the hallucinogen under study, and that effects may vary from not noticeable to extremely strong. This could potentially decrease the disappointment caused by the belief that they did not receive the active drug.

Blinding of participants (and potentially therapists as well) to aspects of study design is another step that has been taken in some cases to minimize the effects of expectancies and bias relating to the belief that the participant received a particular treatment. This does not have to involve actual deception, which would raise serious ethical concerns in the context of administration of hallucinogens. Rather, participants may not be given complete information about the treatments included in the study, the relative probabilities, or the possible orders of treatments. For example, in the Griffiths *et al*. psilocybin study discussed above [44], participants and session monitors were told that participants would have 2 or three sessions, and that they would receive a moderate or high dose of psilocybin in at least one session. They were told that they would receive one of 11other drugs or a low dose of psilocybin in the other sessions. In fact, there were three groups: high-dose psilocybin in the first session and methylphenidate in the second session; methylphenidate in the first session and psilocybin in the second session; or methylphenidate in the first and second sessions, followed by open-label psilocybin in the third session. Session monitors were not able to guess the design of the study under these conditions.

2.6.3. Possible Study Designs for Clinical Trials

Fig. (**1**) illustrates four basic trial designs discussed in this section. Although a simple two-group design may work well if the study treatment involves a single drug administration session, the effects of expectancy are compounded for multiple-session treatments if patients and therapists are able to predict the experience of later sessions based on earlier sessions. For example, if a 2-group 2-session design is used (i.e., both sessions either active medication or control), then this fact would ideally be concealed from both the participants and the therapists. In practice this could be difficult to maintain. A possible solution is to include additional "distractor" groups that receive active medication in only some of the sessions, i.e. group 1 receives active medication in both sessions, group 2 receives the control medication both sessions, group 3 receives control in the first session and active medication in the second session, and group 4 gets active medication in the first session and control in the second session. Groups 3 and 4 could be smaller than the other two since the primary purpose of this is to maintain uncertainty as to what will happen in the second session. It is particularly important that participants not know that they will receive the control medication in the second session; therefore a 3-group design is also feasible: group 1 receives active medication both sessions, group 2 receives control in both sessions, and group 3 gets control medication in the first session and active medication in the second session.

Cross-over designs have been used extensively in early-phase trials, including studies of ketamine in patients with major depressive disorder [164] and bipolar depression [165], and psilocybin in normal volunteers [44]. This design is ideal for studying treatment of conditions in which clinical status tends to be stable over time and is unlikely to change without treatment. It is best for treatments which have effects that are rapidly evident, and preferably reversible. Crossover designs are somewhat problematic in addiction treatment because clinical status can change markedly over relatively short periods of time, independent of treatment, and treatment effects are generally measured over a period of at least 3 months, preferably 6 months or a year. This means that while at the beginning of the first course of treatment all participants might be, for example, outpatients who had been

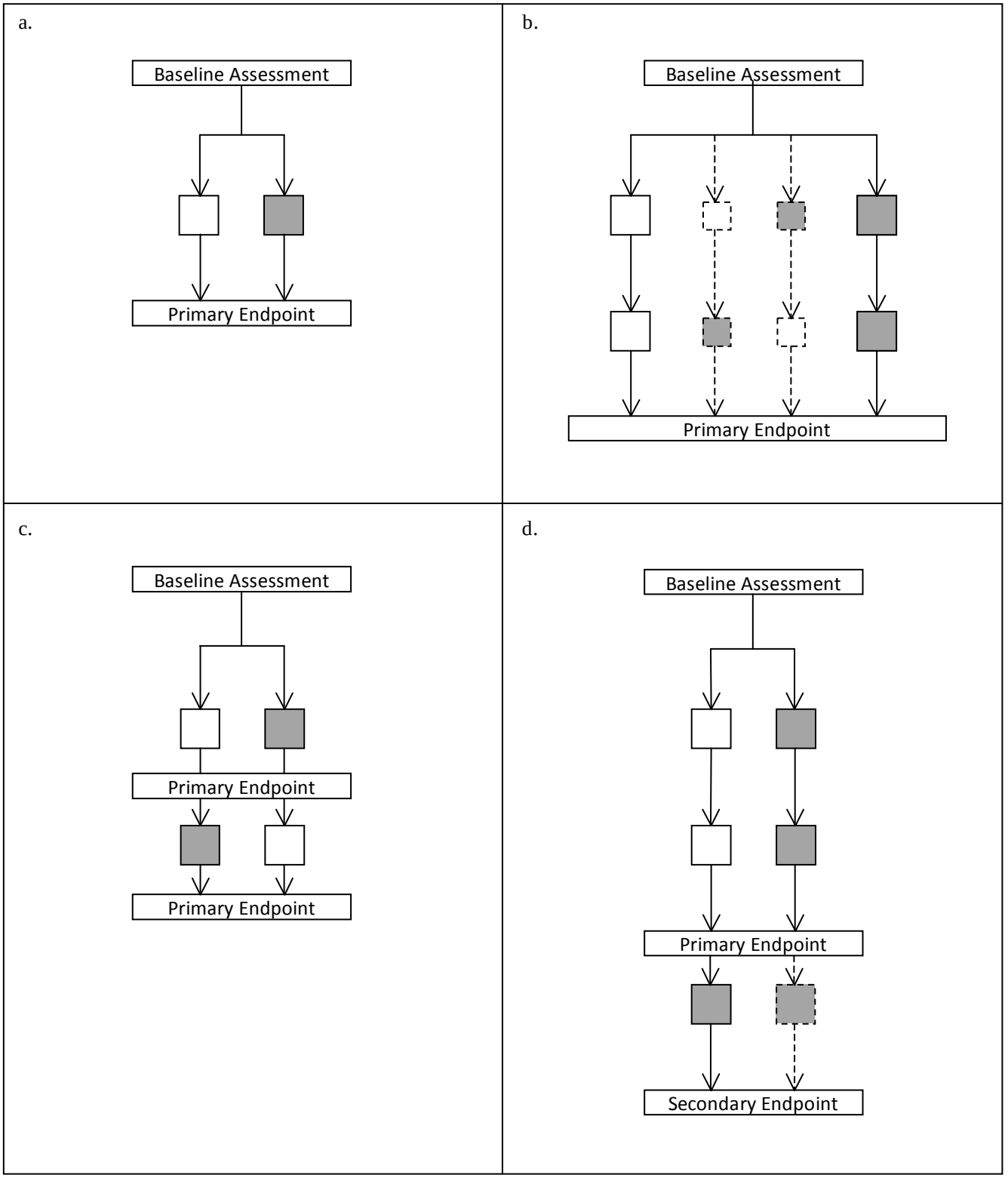

Fig. (1). Possible designs for randomized trials of classic hallucinogens. Dark boxes signify administration of active drug. Light boxes signify administration of control drug. Branch points signify double-blind random assignment. Dashed lines and borders indicate arms that may be omitted in alternate versions of the design. **a**) Single-session, two-group design. **b**) Two-session, two-group design with optional groups receiving one active medication session and one control medication session. **c**) Crossover design. **d**) two-group two session design with open-label phase following endpoint for double-blind phase. See text for details.

drinking regularly during the past month but not using other drugs, 3-6 months later at the start of the second course of treatment some of the participants would be sober, some would be drinking more heavily, some would have been hospitalized, some would be using other drugs, some would be unchanged, and some would have dropped out or been lost to follow-up. These problems are obviated to some extent by crossing over after a shorter time interval such as a week or a month, but this interval is less than ideal to detect a clinically meaningful treatment effect, although it could be sufficient for proof-of-concept studies measuring proximal outcomes such as craving, fMRI changes, etc. A wait-list control can be thought of as a variation of the cross-over design. In this context it has the additional disadvantages that it is not blinded and requires withholding treatment for a treatable condition, which is ethically problematic.

Another possible design variation is to conduct a double-blind trial with 2-4 groups as described above, followed by administration of open-label active drug (perhaps one additional session) for all participants. It would also be possible to offer the final open-label session only to participants who did not receive active medication during the double-blind phase, although this would require breaking the blind for each individual at the end of the double-blind assessment period. The advantages to this design are that demoralization and differential drop-out in the control group would be decreased, and the pre-post effects of active treatment in the control group would be of some interest. The disadvantage is that the between-group comparison would only be valid until the open-label session was conducted. However, this could be extended for a longer period (several months) than in the cross-over design described above since the open label treatment would not be compared to a control condition or included in the primary outcome analysis.

3. DISCUSSION

Existing data justify renewed clinical investigation into the effects of classic hallucinogens in the treatment of alcoholism and other addictions. Preclinical research with classic hallucinogens has demonstrated several effects that could potentially affect addictive behavior, but the behavioral effects of classic hallucinogens have not been studied in animal models of addiction. Studies of classic hallucinogens, including recent rigorous studies with psilocybin in normal volunteers, have demonstrated persisting effects including positive changes in attitude, mood, and behavior. Sacramental use of classic hallucinogens appears to be strongly associated with decreased alcohol and drug use. Although clinical trials from the 1960s were long held to be inconclusive, a recent meta-analysis demonstrated robust statistically and clinically significant improvement in drinking associated with LSD administration in the 6 randomized controlled trials for which data are available. Clinical trials have recently been conducted, are under way, or are planned for indications including obsessive compulsive disorder, anxiety associated with advanced stage cancer, and depression. Open-label pilot studies have now been initiated using psilocybin in the treatment of nicotine dependence and alcohol dependence.

In addition to common design issues such as target population, dose and duration of treatment, choice of outcome variables, and hypothesized mechanisms of change, clinical trials using hallucinogens involve a number of unusual design issues relating to the difficulty of blinding to the subjective effects of the drugs, and the possibility complex interactions between psychological factors (prior to, during, and after drug administration) and the biological effects of the drug. It is possible that drug effects are moderated by psychological state prior to drug administration and mediated by psychological states during and after drug administration. Therefore the management of expectancies and the integration of the psychosocial elements of treatment with the administration of the study medication are of critical importance. The careful assessment of relevant psychological dimensions such as those discussed above, as well as biological effects of the treatment (including neuroimaging) will be necessary to understanding how these treatments affect people.

There are many clinical populations that could be studied and many approaches that could be justified since very little is certain at this point about how to optimize the therapeutic effects of these drugs in the treatment of addictions. If early phase work justifies further study, double-blind controlled trials should be designed bearing in mind the issues of blinding and expectancies that have been discussed. Although there are many possible ways of dealing with these issues, some form of psychoactive but ineffective placebo should be strongly considered. The psychosocial treatment should be designed to maximize the therapeutic benefits of the drug experience, but must also be credible even in the case of a relatively mild drug experience. The differential effects of treatment and control on candidate mechanisms of change should be explored to the extent that is practical. Future research should also examine the effects of both biological and psychological participant characteristics (candidate moderators) on treatment response. The time course of treatment effects should be studied carefully as prior studies suggest that treatment effects become attenuated after 3-6 months. Finally, to guard against the risk of type-two error (which led to the erroneous conclusion that LSD was not effective for treatment of alcoholism in randomized trials), studies should be adequately powered or clearly defined as proof-of-concept studies rather than efficacy trials.

Future Research Questions:

- Well-designed efficacy trials are necessary to determine the effects of classic hallucinogens on alcohol dependence and other substance use disorders, including both magnitude and duration of effect.
- Future research should also address mechanisms of action, including acute and persisting effects in multiple biological and psychological domains.
- In addition, future studies should attempt to identify individual characteristics predicting clinical response.

Key Learning Objectives:

- Several lines of evidence suggest that classic (5HT2A agnoist) hallucinogens may have clinically relevant effects on addictive behavior including alcohol dependence.
- Methodology of clinical trials using classic hallucinogens is complicated by their strong and variable subjective effects.

- Study design in trials employing classic hallucinogens must contend with a number of unusual design issues relating to the difficulty of blinding to the subjective effects of the drugs, and the possibility complex interactions between psychological factors (prior to, during, and after drug administration) and the biological effects of the drug.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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