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Therapeutic mechanisms of classic hallucinogens in the treatment of addictions: from indirect evidence to testable hypotheses

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Alcohol and drug addiction are major public health problems, and existing treatments are only moderately effective. Although there has been interest for over half a century in the therapeutic use of classic hallucinogens to treat addictions, clinical research with these drugs was halted at an early stage in the early 1970s, leaving many fundamental questions unanswered. In the past two decades, clinical research on classic hallucinogens has resumed, although addiction treatment trials are only now beginning. The purpose of this paper is to provide a targeted review of the research most relevant to the therapeutic potential of hallucinogens, and to integrate this information with current thinking about addiction and recovery. On the basis of this information, we present a heuristic model which organizes a number of hypotheses that may be tested in future research. We conclude that existing evidence provides a convincing rationale for further research on the effects of classic hallucinogens in the treatment of addiction. Copyright © 2012 John Wiley & Sons, Ltd.

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Introduction

Hallucinogens comprise several classes of drugs with distinct mechanisms of action including agonist activity at 5HT2A receptors, antagonism of NMDA receptors, kappa opioid receptor agonism, and muscarinic acetylcholine receptor antagonism. This review will focus primarily on the classic hallucinogens, defined for purposes of this review as those agents that have effects similar to those of mescaline, psilocybin, and LSD, and 'principally exert their central nervous system (CNS) effects by an agonist (or partial agonist) action at serotonin (5-HT)2A receptors'.[1]

Hallucinogenic substances have been used in both religious and medicinal contexts for centuries in a variety of different cultures. In the 1950s through the early 1970s there was great interest in the use of classic hallucinogens to facilitate rapid therapeutic effects in alcohol and drug addiction, as well as anxiety, depression, obsessive-compulsive disorder, and other conditions. Many clinicians and centres reported the benefits of hallucinogen use in the context of therapy to facilitate the therapeutic process and strengthen the therapeutic relationship. Psycholytic and psychedelic therapy models of the 1950s through the early 1970s both used hallucinogen-assisted treatment to promote lasting personality change, although they emphasized different processes in bringing about therapeutic effects.[2,3] The psycholytic method used low to moderate doses of hallucinogens to facilitate therapy that was based on traditional psychoanalytic principles.[4,5] The psychedelic method, rather than emphasizing resolution of childhood conflicts or traumatic experiences, used higher doses of LSD with the goal of inducing a 'psychedelic' (mystical) experience, which, it was held, often induced lasting change in habitual patterns of thought, emotional response, and behaviour.[6,7]

Many of the studies from the 1960s, particularly those employing the psychedelic model, reported psychological changes following hallucinogen administration. Unger noted that significant personality change occurred when a 'transcendental' experience occurred during the drug session.[8] Equivocal changes on measures of personality were observed following LSD administration in a randomized controlled study of LSD in normal volunteers conducted by McGlothlin *et al*.[9] Fifty-eight percent of participants reported significant changes after the LSD session, but there was less support for such change on the objective measures used in the study. Mogar and Savage reported clinical outcomes in a sample of outpatients who received a single dose of LSD in the context of psychedelic therapy.[10,11] Follow-up data at two and six months were available for sixty of the seventy patients. Improvements were observed on the clinical scales of the Minnesota Multiphasic Personality Inventory (MMPI) at both time points. Interpersonal Check List scores showed increased assertiveness and interpersonal confidence, and the Value-Belief Q-Sort revealed persistent changes in self-reported values. Extensive positive changes in behavior were also reported. Similarly, Bottrill reported improvements on the clinical scales of the MMPI in a small non-clinical sample of male undergraduates before and one week after an LSD administration session.[12] However, these changes had dissipated at 3-month follow-up.

In the 1950s through the early 1970s, the primary focus of research on the use of hallucinogenic substances in the treatment of addiction was the use of the prototypical classic hallucinogen LSD in the treatment of alcoholism. Over 30 publications during this period reported on the effects of LSD in the treatment of alcoholism,[2,13–16] with more limited research on LSD for the

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treatment of drug addiction.[17] Dipropyltryptamine was studied less extensively.[18,19] Although many of these studies had serious methodological limitations, there were at least a dozen studies with some form of control group.[20,21] With few exceptions, clinical research on hallucinogens was discontinued in the early 1970s, after enactment of the Controlled Substances Act placed all such compounds into the highly restrictive Schedule I class.

A recent meta-analysis[20] examined six randomized trials of LSD for alcohol dependence that reported drinking outcomes.[22–27] These studies all had male inpatient alcoholics as participants and employed a single high-dose LSD session, but they 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. A total of 325 participants received active treatment with LSD, and 211 received control treatment. At first post-treatment follow-up (ranging from 1 month to 12 months) 59% of the LSD-treated participants were significantly improved, *vs* 38% of the control participants (odds ratio 1.96, confidence interval 1.36–2.84, $Z = 3.59$, $p = .0003$). These effects were highly consistent across the six studies. Treatment effects decreased with the duration of follow-up, but remained significant at six months. These robust effects provide a strong rationale for renewed clinical investigation of classic hallucinogens for the treatment of alcoholism and other addictions.

Although there were no further addiction treatment trials with classic hallucinogens for over 30 years, early-stage clinical trials or psilocybin for nicotine dependence[28] and alcohol dependence (NCT01534494) are currently under way. The study of hallucinogens and their effects has advanced considerably in the past two decades, and much of this literature is relevant to the question of whether any of these agents could be of use in addiction treatment. The purpose of this paper is to provide a targeted review of the research on hallucinogens conducted in the past 20 years which is most relevant to their therapeutic potential, and to integrate this information with current thinking about addiction and recovery. On the basis of this information, we will present a heuristic model which organizes a number of hypotheses that may be tested in future research.

Acute and persisting brain effects of classic hallucinogens

Hallucinogens encompass a variety of different compounds with varying pharmacological and behavioural effects. Although the classic hallucinogens, including LSD, psilocybin, mescaline, DMT, and a large number of analogues, all are thought to act primarily at 5HT2A receptors, they are structurally diverse and bind to other receptors as well, including but not limited to a number of serotonin receptor subtypes.[1,29] Classic hallucinogens induce characteristic acute alterations in perception, subjective experiences of reality, and cognitive abilities.[30,31]

Direct effects on serotonin receptors

A considerable body of research has characterized the effects of classic hallucinogens in mammalian cortex. Although classic hallucinogens bind to a considerable number of serotonin receptor subtypes and other receptors including D1 and D3 receptors,[29] the psychoactive effects of all classic hallucinogens are thought to be due primarily to their actions at 5HT2A receptors.[1,32] Stimulation of 5HT2A receptors causes activation of pyramidal cells in cerebral cortex.[33,34] Ketanserin, a 5HT2A antagonist, blocks nearly all subjective effects of psilocybin in humans.[35]

Secondary effects on glutamate and dopamine receptors

Some research indicates that classic hallucinogens may have secondary effects on the glutamatergic system. In rat medial prefrontal cortex, 4-iodo-2,5-dimethoxyphenylisopropylamine (DOI, a classic hallucinogen) induces glutamate release from pyramidal cells projecting onto pyramidal cells in cortical layer V, leading to increased activity of the latter through a process that depends on AMPA receptors.[36] In mouse models, effects of hallucinogenic 5HT2A agonists are mediated by different intracellular signalling cascades than those activated by serotonin and non-hallucinogenic 5HT2A agonists. Unlike serotonin, effects of DOI are not mediated by beta-arrestin-2.[37,38] On the other hand, the effects of LSD are mediated in part by pathways involving pertussis toxin-sensitive $G_{i/o}$ proteins and Src, while the effects of lisuride (a non-hallucinogenic 5HT2A agonist) do not depend on these pathways.[39] Moreno *et al*. propose that the metabotropic glutamate mGlu2 receptor is necessary for the pharmacological and behavioral effects of hallucinogenic 5-HT2A agonists[40]. Psilocybin also increases striatal dopamine concentrations, but haloperidol (an antagonist of D2, D3, and D4 receptors) decreases the euphoria and depersonalization effects of psilocybin by only 30%,[41] and actually increases its psychotomimetic effects,[35] indicating that dopamine is not the primary mediator of these effects.

Persisting changes in the brain

Ultimately, acute drug effects alone cannot account for lasting therapeutic effects. To affect substance use behaviour for weeks or months after administration, an hallucinogen would have to cause persisting changes in the brain. Although these changes are by definition biological, psychological responses to the experience could play a role as well, analogous to the brain changes induced by psychologically traumatic experiences. Very little is known about persisting brain changes related to the administration of classic hallucinogens, but there are animal data suggesting directions for future research. The classic hallucinogen DOI and serotonin increase expression of glial cell line-derived neurotrophic factor (GDNF) mRNA in glioiblastoma cells by a 5HT2A-dependent mechanism.[42] Through its action on 5HT2A receptors, DOI has also been shown to increase levels of brain-derived neurotrophic factor (BDNF) in rat parietal cortex and other neocortical regions.[43] BDNF was decreased in hippocampus (possibly due to stress), and unaffected in piriform cortex. Such effects could potentially lead to changes in synaptic strength in affected regions. These findings are relevant because levels of BDNF or GDNF are inversely related to alcohol consumption and conditioned place preference in animal models.[44] 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.[45,46] Administration of DOI activates intracellular signalling cascades associated with dendritic spine remodelling on rat pyramidal cells, and transiently increases the size of dendritic spines on cortical neurons.[47] At

present there is no direct evidence that any of these mechanisms mediates anti-addictive effects in humans.

Acute and persisting psychological effects of classic hallucinogens

In addition and parallel to their neurobiological effects, hallucinogenic compounds induce marked acute effects in a person's subjective experience. These acute psychological effects have the potential to contribute to lasting changes in the individual, including changes in addictive behaviour. In this section we review studies of hallucinogen effects on three psychological domains that have been studies extensively: mystical experience, mood and affect, and personality. We then discuss the relevance of these domains to addiction and addiction treatment. It should be noted that the psychological effects of hallucinogenic compounds are believed to be influenced significantly by both the mental 'set' of the individual prior to hallucinogen consumption and the setting in which the hallucinogen is taken. The wide range of inter- and intra-individual differences reported in hallucinogen-induced experiences may in part be a result of variability in set and setting. The impact of both external and internal factors was investigated in many of the early studies.[9,10,48,49] In order to induce the desired acute psychological effects believed to help treat addiction, both factors must be taken into consideration.

Mystical experience

'Mystical experience' refers to a particular class of conscious states that can occur under a variety of circumstances and which are often, but not necessarily, understood in religious terms. Several overlapping definitions have been proposed since William James treated the topic in *The Varieties of Religious Experience*.[50] Drawing on the work of Stace,[51] Pahnke *et al.* defined mystical experiences by the presence of the following 6 characteristics: (1) sense of unity or oneness (loss of usual sense of self as a separate entity); (2) transcendence of time and space; (3) deeply felt positive mood; (4) sense of wonder and awe (sacredness); (5) meaningfulness (noetic quality) ; and (6) ineffability (claim of difficulty in describing the experience in words).[26] This definition and been widely used in research on effects of classic hallucinogens, and forms the basis of the Pahnke-Richards Mystical Experience Questionnaire.[52,53] As described below, hallucinogens have been observed to induce mystical experiences within research settings as well as in the context of religion.

Mystical experience and after-effects in research contexts

The potential for hallucinogens to induce mystical experiences has been well-documented within research settings. There is strong evidence from rigorous quantitative studies by Griffiths *et al.*[54,55] that psilocybin can occasion profoundly meaningful experiences that have significant lasting effects. Twenty-two out of 36 participants receiving a single high-dose psilocybin session reported a 'complete mystical experience', defined as a score of at least 0.6 on 6 subscales of the Pahnke-Richards Mystical Experience Scale.[54] Fourteen months after the psilocybin session, 67% of participants rated it as one of the five most significant spiritual experiences of their lives, and 61% reported that the experience was associated with 'moderate to extreme positive behavioural change', as well as positive changes in attitudes, mood, and altruism.[83] In addition, these self-reports were correlated with ratings by community observers who reported similar positive changes in participants. Scores on the Hood Mysticism Scale[56] immediately after the psilocybin session were strongly related to participant ratings of spiritual significance and personal meaningfulness 14 months later (correlation coefficients ranging from .61 to .78). 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 two highest doses.[55] Persisting positive effects one month after the psilocybin session were found to be dose related. In another recent human administration study, the hallucinogen MDA was also reported to induce mystical experiences (Hood Mysticism Scale) in participants.[57] Compared to the placebo condition, MDA induced significant elevations on all three of the sub-scales: Introvertive Mysticism, Religious Interpretation, and Extrovertive Mysticism.

Hallucinogen use in formal religious contexts

Classic hallucinogens have been used ceremonially and religiously for centuries (for comprehensive references on this topic see Roberts and Hruby,[58] current version available on-line at http://csp.org/chrestomathy/a_chrestomathy.html). Cross-sectional studies have consistently shown decreased rates of alcohol dependence among members of religions that use classic hallucinogens as a regular part of their practice, including the Native American Church, which uses the mescaline-containing peyote cactus as a sacrament,[59] and both Brazilian[60] and US[61] sects using ayahuasca. Although cultural norms within these religions likely contribute to such effects (use of alcohol and drugs is strongly proscribed), the pattern suggests the possibility of a pharmacological effect as well.

Ayahuasca is an hallucinogenic tea made from plants containing DMT and beta carboline alkaloids. The beta carbolines (including harmine, harmaline, and tetrahydroharmine) are reversible monoamine oxidase inhibitors, rendering the DMT orally active. Ayahuasca is used sacramentally by a number of organized religions, of which the União do Vegetal and Santo Daime are the best known. In an assessment of mental health among ritual users of ayahuasca, Fabregas found ayahuasca users had lower scores on the Addiction Severity Index (ASI) alcohol use and psychiatric subscales compared to a control group.[62] Halpern *et al.* interviewed 34 American Santo Daime members regarding effects of church participation.[61] Participants reported a wide variety of psychological benefits. Of 24 members with a history of substance use disorder, 22 were in full remission, and all 5 who had a history of alcohol dependence reported that church involvement played a pivotal role in their recovery. Trichter *et al.* evaluated self-reported spiritual changes among novice participants after an ayahuasca ceremony.[63] Although the measures used to assess spiritual change following the ceremony, the Hood Mysticism Scale and the Spiritual Well-being Scale,[64] were not significantly different from baseline levels, a positive relationship was observed between the two scales and the Peak Experience Profile (derived from Pahnke's original questionnaire[65] and measuring the intensity of the altered state experienced during the ceremony).[63] In addition, a qualitative analysis of participants' experiences was performed, and a consistent 'spiritual themes' were identified in many of the participants' reports of the experience.[63]

The peyote cactus, containing psychoactive quantities of the classic hallucinogen mescaline, has been used ceremonially by

native North Americans for at least 5500 years,[66] and is currently used extensively by groups including the Native American Church (NAC)[67] and the Huichol of northern Mexico.[68] Although there are few hard data, many have suggested that taking peyote in a religious context helps alcoholics achieve sobriety.[69] Albaugh and Anderson reported the use of peyote in the treatment of alcoholism in the NAC.[70] The authors surveyed 165 individuals who received peyote in the treatment of alcoholism from 1972 to 1974. They reported a 7–10-day period following the peyote ceremony in which participants display increased openness and willingness to communicate. These authors suggested peyote's 'facilitation of cathartic expression' may contribute to its efficacy as a treatment for alcoholism. In contrast, Garrity suggested that introspection elicited through the peyote ceremony fostered self-examination, re-evaluation, and ultimately a greater understanding of one's self that in turn enhanced motivation for sobriety.[71]

Halpern *et al*. assessed the cognitive and psychological effects of long-term peyote use by members of the NAC.[72] There were no significant differences in performance on a variety of neuropsychological tests between the peyote group and a non-substance-using comparison group.[72] Further, the peyote group scored significantly better on the General Positive Affect and Psychological Well-being scales of the Rand Mental Health Inventory (RMHI). Additionally, log-transformed lifetime peyote use was associated with a significantly higher score on the Mental Health Index of the RMHI, and significantly lower scores on the Anxiety and Loss of Behavioural/Emotional Control scales of the RMHI. A third group of former alcoholics scored worse than the control group on a number of psychological and neuropsychological measures. This study does not provide information on the prevalence of alcoholism among NAC members *vs* controls because current and former alcoholics were excluded from both groups.

Relationship of mystical experience to addiction and recovery

Over 100 years ago, William James described the phenomenon of sudden change in the form of religious 'conversion'[49] which was often accompanied by changes in behaviour such as the abrupt onset of sobriety in alcoholics. More recently, William R. Miller and others have elucidated the nature of what has been termed 'quantum change', which is conceptualized as overlapping considerably with mystical experience.[73] Sudden and lasting behaviour change can be triggered by an acute experience that is vivid, unexpected, (usually) benevolent, and mystical and/or characterized by important insights. These experiences are frequently but not always described as religious or spiritual in nature.

Twelve-step programmes such as Alcoholics Anonymous (AA) are based on the model that spiritual change can bring about recovery from addiction.[74] There is some evidence that experiencing a spiritual awakening may be a significant predictor of abstinence. The term 'spiritual awakening', contained in the 12th step of AA, refers to a life change 'amounting to a new state of consciousness or being' through the grace of a higher power, and leading to a new capacity for 'honesty, tolerance, unselfishness, peace of mind, and love'.[75] The paradigmatic spiritual awakening was experienced by AA founder Bill W. during treatment with the deliriant hallucinogen belladonna, and was a typical mystical experience.[76] Such experiences figure prominently in the AA literature,[77] and are not uncommon.[78] In a large (n = 587) alcoholism treatment sample, reporting a recent spiritual awakening was associated with markedly increased rates of 12-month continuous abstinence (odds ration = 3.9).[79] In another study, 82% of individuals who reported a spiritual awakening between baseline and follow-up reported abstinence compared to 55% of those not reporting such an experience (55%) ($X2 = 26.48$, $p < 0.001$).[80] A recent mediational analysis demonstrated that changes in religiosity/spirituality (measured by the Religious Background and Behaviour instrument)[81] partially mediates the effects of AA involvement on abstinence.[82] This study does not demonstrate whether spiritual awakening played a role in these changes.

Mood and anxiety

Mood and anxiety disorders often co-occur with substance use disorders. Several recent studies have quantified the effects of psilocybin on anxiety and mood. Ketamine has been shown potential to improve symptoms of depression in several studies, and MDMA may decrease symptoms of post-traumatic stress disorder (PTSD). Here we review the recent psilocybin studies, followed by a brief review of the studies involving non-classic hallucinogens.

Effects of psilocybin on mood and anxiety

Although not designed as clinical trials, recent studies by Griffiths *et al*. of psilocybin in normal participants have provided evidence that psilocybin can cause persistent enhancement of mood[54,55,83]. Participants in the psilocybin group reported a significantly greater change in positive mood two months following the drug session compared to the active-control group.[54] The improvements in mood reported by participants in the psilocybin group remained significant at a 14-month follow-up visit.[83] Participants in the psilocybin group also reported significantly increased current personal well-being or life satisfaction two months after the session when compared to the active control group.[54] Likewise these changes remained significant at the 14-month follow-up visit.[83] The positive mood changes following the psilocybin session showed a dose-related pattern, with increased psilocybin dose associated with increased reports of positive mood change.[55] Dose-related increases in sense of well-being or life satisfaction and positive attitudes about one's life and oneself was observed as well.

Two published studies have explored the effects of psilocybin in anxiety disorders. The effect of varying doses of psilocybin (doses up to 0.3 mg/kg PO) on symptoms of obsessive compulsive disorder was tested in nine subjects in a within-subjects design.[84] All doses tested produced significant decreases in obsessive-compulsive disorder (OCD) symptomatology, but there was no effect of dose or dose-by-time interaction. Using a double-blind, cross-over design, Grob *et al*. administered psilocybin 0.2 mg/kg vs. placebo to 12 patients with anxiety related to advanced cancer.[85] Although significant treatment effects were not demonstrated in this pilot study, there were statistical trends suggesting a positive effect of psilocybin on mood. The low dose used may have limited efficacy in this study. Additional clinical trials are currently under way in cancer patients.

Effects of non-classic hallucinogens on mood and anxiety

Ketamine produces rapid and robust antidepressant effects in patients with treatment-resistant major depression and bipolar depression.[86–92] These effects last a week or more, and may be related to increased activity at AMPA receptors relative to NMDA receptors.[93,94] Interestingly, stronger antidepressant effects are found in those with family history of alcohol dependence.[95]

MDMA is not a classic hallucinogen as it does not have significant affinity for 5HT2A receptors.[29] It acts primarily by causing presynaptic release of serotonin and dopamine, although some of its effects appear to be mediated by increased activity of serotonin at 5HT2A and other serotonin receptors.[96] It has strong stimulant effects, and has effects on perception and cognition that are much less prominent than those of the classic hallucinogens.[97,98] In addition, some investigators believe that it has 'empathogen' effects that are distinct from those of both stimulants and classic hallucinogens.[99] In a double-blind placebo controlled pilot study investigating the efficacy of MDMA in the treatment of PTSD, 20 individuals diagnosed with PTSD (12 participants in the MDMA group and 8 individuals in the placebo group) took part in 2 drug administration sessions and 11 psychotherapy sessions.[100] The MDMA group showed 83% clinical response to treatment compared to 25% in the placebo control group at follow-up two months after the second drug administration session (Clinical response was defined as greater than 30% improvement from baseline on the Cardiff Anomalous Perceptions Scale (CAPS)).[100]

Relevance of mood and anxiety to addiction

Mood and anxiety disorders increase the risk of substance use disorders. Data from the NESARC study demonstrated strong associations between substance use disorders and mood and anxiety disorders.[101] For example, the odds ratio for alcohol dependence and any mood disorder was 4.1, and the odds ratio for alcohol dependence and any anxiety disorder was 2.6. The odds ratio for drug dependence and any mood disorder was 12.5, and that for drug dependence and any anxiety disorder was 6.2. The temporal sequencing of these disorders is variable and probably differs depending on the particular disorders being considered, making it difficult to generalize about the direction of causal relationships.[102–104] Although the self-medication hypothesis[105] is a common explanation, the actual processes accounting for this comorbidity have been elusive.

Negative affective states are established as a risk factor for relapse.[106–108] To the extent that addictive behaviour is driven by mood and anxiety symptoms, one would expect that decreasing such symptoms would increase the probability of improvement in addictive behaviours. There is some evidence that treatment of anxious alcoholics with buspirone has beneficial effects on drinking behaviour.[112] Although animal studies have supported the use of antidepressants to decrease ethanol consumption,[113] studies of antidepressant treatment in depressed alcoholics and drug addicts have yielded mixed results,[109–111] possibly due to the limited effectiveness of antidepressants in these populations. A meta-analysis by Nunes and Levin reported a modest positive effect of antidepressants in the treatment of patients with comorbid depressive and substance-use disorders.[111] Another meta-analysis assessed the efficacy of antidepressants in the treatment of substance use disorders with and without comorbid depression.[110] The use of antidepressants to treat substance use disorders was supported only for nicotine dependence, regardless of comorbid depression diagnosis. The authors concluded the use of antidepressants to treat alcohol dependence without comorbid depression was not justified, while, the use of antidepressants to treat cocaine dependence without comorbid depression was inconclusive.[110] The authors further concluded that evidence on the use of antidepressants to treat alcohol, opioid, or cocaine dependence with comorbid depression was mixed, and future studies were warranted.[110] In a review of treatment for cocaine dependence and depression, Rounsaville noted negative results were found in studies assessing selective serotonin reuptake inhibitors (SSRIs), while some positive findings were found in studies using desipramine or buproprion.[109] Further details on the use of serotonergic agents in alcoholism are found in the section on craving below.

Personality

Effects of classic hallucinogens on personality

Many of the initial hallucinogen studies reported changes on measures of personality following hallucinogen administration. Important work from the 1960s in this area is summarized in the introduction to this paper. There has been minimal research in the past 20 years investigating these mechanisms. However, Maclean *et al*. recently reported changes in personality following a single session of psilocybin.[114] More specifically, the dimension of Openness was increased ($M = +2.8$, $F(1, 51) = 5.47$, $p = 0.023$, $\eta_p^2 = 0.10$) in individuals who achieved a complete mystical experience. At a 16-month follow-up Openness remained significantly higher than at baseline.[114] These findings support the hypothesis that administration of classic hallucinogens can produce positive changes in personality.

Relevance of personality to addiction

Although there is no such thing as an 'addictive personality', specific patterns of personality traits have been observed in substance-using populations. A recent meta-analysis of 20 studies found alcohol use was associated with increased Neuroticism and decreased Conscientiousness and Agreeableness.[115] In another recent meta-analysis, the authors characterized the substance use disorder profile as low in Conscientiousness and Agreeableness, with relatively weak effects on Neuroticism and Extraversion.[116] In a sample of 2676 male veterans seeking substance abuse treatment, substance users were more neurotic (88th percentile), less open (39th percentile) less agreeable, and less conscientious (both below the 20th percentile) than a non-clinical normative sample.[117] Additional recent studies have provided further evidence for the association of addiction with decreased conscientiousness,[118,119] increased extraversion,[118,120] increased neuroticism,[118] and decreased openness.[118] A 16-year prospective study ($n = 489$ college freshmen) also demonstrated that increases in conscientiousness and decreases in neuroticism over time were associated with decreases in drinking problems.[121] These personality traits have generally been thought of as contributing causally to risk for substance use disorders. However these studies are correlational and cannot rule out the possibility that these traits were at least in part induced by substance use and improve due to abstinence.

Personality traits in patients with addictions may be affected by treatment and affect treatment outcome. Piedmont assessed personality change among patients completing drug rehabilitation. Personality changes on all five domains of personality were observed at completion of treatment when compared to baseline.[122] Changes in Neuroticism, Agreeableness, and Conscientiousness remained significantly different from baseline at a follow-up visit approximately 15 months after treatment.[122] Bottlender and Soyka assessed personality traits in 74 patients that had completed substance use treatment.[123] Patients who had relapsed at the six-month follow-up visit (20% of the sample)

had significantly lower scores on Conscientiousness ($t = -2.049$, $P < 0.04$) and Extroversion ($t = 1.729$, $P < 0.01$) at the beginning of treatment.[123] Conscientiousness was lower ($t = -2.092$, $p < 0.04$) and Neuroticism was higher ($t = 2.250$, $P < 0.02$) in those who had relapsed at 12 months.[123] In another study of personality change during recovery from addiction, personality factors associated with treatment completion and drop-out were assessed. Patients who dropped out of treatment scored significantly lower on the Temperament and Character Inventory (TCI) scales Persistence and Novelty-Seeking at the start of treatment.[124] Women who completed treatment showed a significant reduction in Neuroticism and Harm Avoidance, and a significant increase in Self-Directedness following treatment.[124]

Finally, personality traits appear to have significant relationships to constructs more directly related to addictive behaviour, such as craving and self-efficacy. Zilberman *et al*. assessed the impact of 'personality styles' on self-reported craving in an all-female sample.[125] Craving scores were significantly correlated with factors on the NEO (Conscientiousness (standardized $\beta = -.285$; $p = 0.005$), and Agreeableness (standardized $\beta = -.215$; $p = 0.017$)) and factors on the TCI (Novelty-Seeking (standardized $\beta = .315$; $p < 0.001$) and Persistence (standardized $\beta = -.221$; $p = 0.013$)). All of these traits are associated with impulsivity.[125] McCormick *et al*. examined the relationship of personality dimensions to response to substance use 'triggers', self-efficacy, and coping strategies.[117] Neuroticism, Conscientiousness, Agreeableness, and Extroversion were all correlated with response to specific substance use triggers including negative emotional states, social rejection and tension.[117] Higher levels of Conscientiousness, Agreeableness, and Extroversion were associated with greater confidence in the ability to refrain from substance use.[117] Neuroticism, however, was associated with a lack of confidence to refrain from using.[117] Individual personality dimensions were also significantly related to specific coping styles. Specifically, Neuroticism was positively associated with escape-avoidant coping.[117] A more recent study similarly found that the strategy of coping through substance use was positively associated with Neuroticism ($r = .28$) and negatively associated with Agreeableness and Conscientiousness, ($r = -.18$).[126]

Established change mechanisms in addiction

A variety of mechanisms have been proposed to mediate recovery from addictions. Three mechanisms that are well-established and potentially modifiable through therapeutic use of classic hallucinogens are reduced craving, enhanced self-efficacy, and increased motivation. Below we discuss how these mechanisms are thought to function, and how they could in principle be activated as a result of hallucinogen treatment. Social support for abstinence *vs*. drinking is another well-established change mechanism, particularly in the context of AA.[127] This mechanism will not be discussed here because clinical administration of hallucinogens could affect social networks only very indirectly. However, social support for abstinence could be important in the context of religions that use hallucinogens sacramentally given the strong value they place on abstinence.

Craving and its brain correlates

Craving is a multi-dimensional construct which includes motivational, affective and cognitive components.[128] Craving research typically elicits the craving phenomenon via exposure to stimuli that increase relapse risk including: stress, a priming dose of the substance of abuse, or stimuli associated with the substance. Neuroimaging approaches studying the effect of such stimuli on brain activity have demonstrated a variety of changes in the response of drug and alcohol addicts' brains to these stimuli, which are related to craving and contribute to relapse.[129,130] Many (though not all) studies have demonstrated a positive relationship between craving intensity and relapse.[123,128,131–135]

Neuronal pathways associated with craving have been assessed through animal research and neuroimaging techniques in humans. Research has identified several brain regions believed to comprise the brain's reward system, including the ventral striatum and nucleus accumbens. Several neurotransmitter systems associated with the brain's reward system, the dopaminergic, glutamatergic, opioidergic, and serotonergic systems, are believed to play a role in the phenomenon of craving and response to drug cues.[136,137] Dopamine release in the mesolimbic dopamine reward system, in particular the nucleus accumbens, has been observed following administration of all drugs of abuse,[136] although there have been PET studies that failed to find this effect with administration of opioids[138] or alcohol.[139] Notably, cues associated with the drug can also elicit this increase in dopamine. It is believed that the mesolimbic dopamine system is responsible for the 'wanting' process associated with the reward system.[136] The striato-thalamo-orbitofrontal circuit has been implicated in goal-directed behaviour and may also be relevant for addiction.[136] Cues associated with the drug of abuse cause increases in brain dopamine levels through classical conditioning. Dopamine draws the person's attention to events that predict a reward to follow.[140] If the anticipated reward does not follow the cue, there is an acute decrease in dopamine release.[136] Serotonergic neurotransmission is involved in the modulation of craving.[137,141,142] Serotonin may also play a role in the attentional processes associated with addiction, and attentional bias towards the drug and related cues could play a significant role in craving and relapse.[140] The serotonergic system regulates motivational and appetitive behaviours that may contribute to addiction.[143] Serotonin regulates reward-related behaviours and is as important in reward processing as dopamine.[144] Serotonin also plays an important role in impulse control and inhibitory processes that are impaired in addiction.[145] Medications that increase central serotonergic activity could theoretically reduce craving and relapse.[145] In the animal models of alcohol abuse and dependence, ethanol consumption decreased as serotonergic activity increased, and consumption increased with reductions in serotonergic activation.[113]

Serotonergic drugs have been studied extensively in the treatment of alcoholism. SSRI antidepressants, although not effective in the treatment of alcoholism [146–148] except for possibly some type A alcoholics [149] and those with co-occurring depression,[150] appear to decrease craving for alcohol under some circumstances. SSRIs appeared to reduce craving in heavy drinkers and mildly alcohol dependent subjects in short-term studies,[151–154] but longer-term studies in more severely alcohol-dependent samples have not demonstrated such effects.[146,148] Other serotonergic agents have been shown to reduce overall drinking but not craving.[143] Ondansetron, a 5HT3 antagonist, has been shown to improve drinking outcomes in early-onset alcoholics and those with the LL genotype of the serotonin transporter.[155,156] Ondansetron was found to reduce craving in early onset alcoholics but to increase craving in late onset alcoholics.[157]

How hallucinogen treatment could work to reduce craving

Past clinical trials have not reported on the effects of classic hallucinogens on alcohol or drug craving, and future trials should include assessment of craving to determine whether there is an effect. At present we can only speculate as to possible mechanisms by which craving could be diminished. Stimulation and persistent activation of serotonergic pathways could affect craving by diminishing attentional bias, normalizing stress response, improving mood, or diminishing anxiety. Persisting brain changes induced by acute brain stimulation during intoxication could modify established patterns of response in brain networks underlying craving. The treatment could potentially disrupt conditioned responses or otherwise alter the individual's response to drug cues leading to reduced craving and consequently a reduction in likelihood of relapse. Additionally it is possible personality changes could affect craving as personality has previously been linked to craving.[125]

Self-efficacy

According to Bandura, efficacy expectancy is the 'conviction that one can successfully execute behaviour required to produce the outcomes'.[158] Self-efficacy provides a means to predict and understand psychological changes that occur during treatment. Bandura concluded that self-efficacy beliefs 'determine' how people feel, think, motivate themselves, and behave.[159] Bandura identified four processes in which self-efficacy beliefs accomplished the above: cognitive, motivational, affective, or selective processes.[160] In alcohol treatment, Bandura suggested one must 'address client's sense of efficacy to control drinking and their outcome expectancies about how they weight benefits of sobriety against costs of severing activities and friends associated with a drinking lifestyle'.

Research on change processes in addiction confirms that the individual's belief in his or her own ability to stop using the drug is a significant predictor of treatment outcome. In a recent review of self-efficacy and addiction, Kadden and Litt remarked that many studies have demonstrated a strong relationship between self-efficacy and substance use outcomes.[161] The quantity and frequency of alcohol or drug consumed has been predicted by self-efficacy, suggesting that self-efficacy could be a mediator in treatment.[161] Oei *et al*. found that drinking refusal self-efficacy was a significant predictor of alcohol consumption in a community sample, while general self-efficacy was a significant predictor of drinking in a clinical sample.[162] Abstinence self-efficacy was a strong predictor of alcohol use one year following alcohol treatment in Project MATCH.[163] Additionally, self-efficacy was found to be a partial mediator in the effect of AA attendance and consequently, abstinence.[164]

One of the guiding principles of Motivational Interviewing is supporting self-efficacy. Bandura identified four ways in which self-efficacy affects motivation. Self-efficacy beliefs determine what goals the individual sets, the amount of energy expended on the goal, the amount of time spent on achieving the goal despite challenges, and resilience to failure.[158] Thus, enhanced self-efficacy could result in improved motivation for abstinence.

How hallucinogen treatment could work to enhance self-efficacy

There are several possible pathways by which hallucinogenic drug administration could lead to enhanced self-efficacy. Having had a mystical experience may encourage the subject to be accepting of the possibility of change. As previously mentioned, self-efficacy has been associated with specific personality dimensions.[117] Conscientiousness, Extroversion, and Agreeableness were positively associated with confidence to refrain from substance use, while Neuroticism was negatively associated with ability to refrain from substance use.[117] Thus, personality changes could reduce substance use by increasing self-efficacy. Improved mood could also promote a generally more optimistic outlook in which self-efficacy is enhanced. According to Bandura, positive mood enhances one's perception of self-efficacy, while negative mood reduces one's perception of self-efficacy.[159]

Motivation to change

DiClemente *et al*. define 'motivation' as referring to 'the causes, considerations, reasons, and intentions that move individuals to perform certain behaviours or sets of behaviour'.[165] Further, 'Motivation influences patients to seek, complete and comply with treatment and to make successful long term changes in drinking.' According to the Transtheoretical Stages-of-Change Model, intentional behaviour change is a multi-dimensional process. This process involves stages of change that can be conceptualized as a temporal dimension with inherent motivational components.[165,166] A second dimension of change involves 10 (or 12) identifiable processes that promote movement through the stages of change.[165,166] The third dimension of change is levels of change, which includes complicating problems in different areas of the individual's life.[166] Processes hypothesized to potentially be invoked during treatment include: consciousness raising, self-reevaluation, self-liberation, dramatic relief, and environmental reevaluation.[165] According to the theory of cognitive dissonance, when an individual's values conflict with behaviour, the individual experiences a drive to reduce the conflict by changing attitudes, beliefs or behaviours.[167] This concept is also applied during Motivational interviewing (MI).

MI and motivational enhancement therapy (MET) are empirically based interventions used in substance abuse treatment that rely on increasing the individual's motivation to change their behaviours and become sober. Behavioural change is elicited through a process of exploration and eventual resolution of ambivalence regarding the behaviour to be changed.[168] Rollnick and Miller defined the technique as a '. . .directive client-centred counselling style for eliciting behaviour change by helping clients to explore and resolve ambivalence'.[168] The style of motivational interviewing is used in MET, which is a brief structured therapy based on MI. A specific active ingredient of MI appears to be the eliciting of client speech in favour of change (called 'change talk'),[169] including statements of desire, ability, reason, need, and commitment to change.[170]

How hallucinogen treatment might work to increase motivation

Hallucinogen treatment could enhance motivation through several of the processes described above, including mystical experience, personality change, and enhanced self-efficacy. It is possible that aspects of the subjective experience during hallucinogen intoxication (e.g. mystical or other novel psychological experiences or insights) can lead to increased motivation to change through (1) increased belief in the possibility of change (enhanced self-efficacy), (2) a heightened awareness of negative consequences leading to increased motivation to change, or (3) a change in perspective leading to increased desire to change. During the hallucinogen session, the individual's own desires

related to sobriety might become more salient, and the discrepancy between his or her values and goals and substance use behaviour could become more apparent. Further, the individual's outlook on life, his place in his environment, his values, etc., could be altered during and after the session.

Relevant research using non-classic hallucinogens in the treatment of addiction

Ibogaine

Ibogaine is an hallucinogenic alkaloid found in several plants, most notably in the root of the Tabernanthe iboga, used for medicinal and spiritual purposes by the indigenous people of Western Africa.[171] Ibogaine is not a classic hallucinogen by our definition because although it acts at 5HT2 and 5HT3 receptors, it also inhibits the serotonin transporter and acts at NMDA, mu, kappa and sigma opioid, and muscarinic and nicotinic cholinergic receptors.[172] Ibogaine attracted the interest addiction researchers when heroin addicts reported that they lost the desire to use heroin after taking ibogaine. Although initial preclinical and clinical results in the treatment of opioid withdrawal were encouraging, this line of research was eventually discontinued due to toxicity concerns.[172–175] Currently there is interest in developing related molecules that are less toxic.[172,173]

Preclinical work suggests that ibogaine may have anti-addictive effects across several classes of drugs.[171,172] Ibogaine administration was associated with reduced self-administration of morphine and cocaine and was found to reduce motor activity elevated following administration of stimulants. Ibogaine has also shown potential in animal models of alcoholism. Reduced ethanol self-administration in rats following administration of ibogaine has been shown to be mediated via increased GDNF in the ventral tegmental area.[176] Noribogaine, but not the ibogaine derivative 18-MC, appears to have similar mechanism of action.[177] Preclinical research suggests GDNF may be a potential target for future pharmacological interventions for addiction.[43,178–180]

Ketamine

A second promising non-classic hallucinogen in the treatment of addiction is ketamine. Ketamine has been investigated in Russia as a potential treatment for both alcohol dependence and heroin dependence. Although ketamine is an NMDA receptor antagonist rather than a classic hallucinogen, recent research reveals considerable overlap in the brain effects of these two classes of drugs.[32] In a controlled but non-randomized study, alcohol-dependent subjects who volunteered to receive ketamine-assisted psychotherapy (ketamine 2.5 mg/kg IM, a dose producing prominent hallucinogen effects) showed significantly higher rates of abstinence at one year (73/111 = 65.8%) than those receiving usual care in the same facility (24/100 = 24%).[181] The psychotherapy used in this study included aspects of both existential psychotherapy (focused on meaning and purpose) and psychodynamic psychotherapy (seeking to discover unconscious roots of the alcohol problem), and emphasized the importance of having a strong psychedelic experience. The ketamine sessions also included exposure to the smell of alcohol during the height of the experience, which was intended to increase the participant's aversion to alcohol. In a randomized, double-blind trial (n = 70), heroin-dependent patients assigned to a single session of ketamine 2 mg/kg IM had significantly higher abstinence rates over 24 months of follow-up than those who received a lower, mildly psychoactive dose.[182] Both groups showed significantly decreased depression and anxiety for at least six months, but participants in the high-dose condition demonstrated greater and more enduring reductions in heroin craving. In a second study (n = 53), patients receiving 2 or 3 ketamine sessions had higher abstinence rates over one year of follow-up (50% continuous abstinence at one year) than those who received one session (22% continuous abstinence).[183] The therapy used in these heroin studies did not include exposure to drug-related stimuli during the experience. Off-label use of ketamine for alcohol dependence has been reported in the USA, but quantitative outcome data are not available.[184]

Discussion

Recent research has demonstrated that administration of hallucinogens can mobilize biological and psychological processes that are relevant to addictions and provide possible mechanisms by which these drugs could promote recovery when administered in an environment and therapeutic context designed to maximize the therapeutic effects of the experience. In particular, mystical experiences can be reliably produced and lead to persisting changes in mood, personality, and behaviour. Animal models of hallucinogen effects provide mechanisms by which classic hallucinogen administration could produce persisting neural changes that could underlie such psychological change. Clinical studies of hallucinogens in other classes (ketamine and ibogaine) indicate probable anti-addictive effects, although further studies would be necessary to confirm these findings and determine their clinical significance. Recent human research with classic hallucinogens also demonstrates that they can be used safely in the context of clinical research.[185]

In spite of these advances, the current generation of research on classic hallucinogens does not yet include clinical studies in addiction populations, and therefore has not yet produced any new direct evidence of clinically relevant effects on addictions. Pilot studies currently underway in nicotine dependence and alcohol dependence will provide a first step in addressing these questions using modern clinical trials technology and building on the current generation of human and basic research on classic hallucinogens.

Conceptual model for research on addiction treatment using classic hallucinogens

Given the relative lack of objective information about the clinical effects of classic hallucinogens in addiction treatment, we have developed a model including possible mechanisms and pathways of action through which administration of an hallucinogen might lead to reduced substance use. Although it is unlikely that all of the elements of this model will ultimately be found to have significant relationships, the paths in this model represent testable hypotheses which can be examined and confirmed or rejected in turn. Figure 1 provides a model including four levels: the treatment and its context, the acute effects of the treatment, persisting general effects of the treatment, and specific end effects that are directly related to changes in addictive behaviour.

The treatment situation will necessarily include the hallucinogenic substance, the patient, and the setting in which the hallucinogen is administered. The specific substance used, the

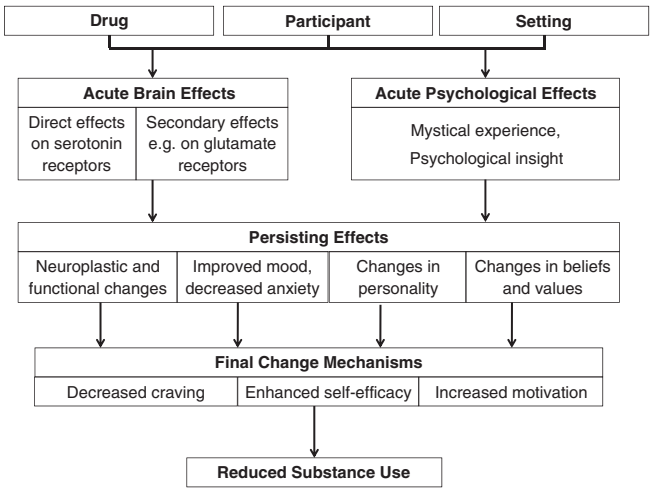

Figure 1. Model of Possible Change Mechanisms in Hallucinogen-Assisted Treatment of Addictions.

dose, and the mode of administration are all obviously important determinants of the experience and its effects. Given the variability in experience induced by hallucinogens it is believed patient characteristics as well as the setting in which the experience occurs can influence the experience for the participant.[185] The individual characteristics of the participant, including the participant's mental set prior to drug administration, particular psychological characteristics and personal history, as well as physiological and genetic factors will influence how the participant responds to the treatment. Lastly, the setting in which the hallucinogen is administered will affect the treatment outcome. The therapeutic model employed, the physical environment in which the hallucinogen is administered, and the therapists present during the administration are all relevant variables.

The acute effects induced by the hallucinogen-assisted treatment have a physiological dimension – the direct effect of the intervention on the brain; and a psychological dimension – the subjective experience reported by the individual. These effects are measured and described by different methodologies although they relate to a common underlying process. Although it is not possible to separate psychological effects from the underlying brain activity, explanatory models based on the former higher-level effects may be at least as useful as more basic explanations, in the same way that chemistry and electrophysiology may provide a more useful model of brain activity than that provided by physics alone. The acute brain effects include direct effects mediated by serotonin receptors and secondary effects on glutamate receptors. The acute psychological effects include mystical experiences and other intense psychological experiences which are often held as highly meaningful by those who experience them.

The acute effects could lead to a variety of potential persisting effects that are of relevance to eventual changes in addictive behaviour. We have reviewed evidence that administration of hallucinogens can result in persisting improvement in mood and reduction in anxiety, changes in beliefs and values, and even personality changes. These psychological changes would necessarily be associated with persisting brain effects (neuroplastic changes and functional changes), although there are currently no data on persisting changes in brain structure or function in humans undergoing hallucinogen-facilitated treatment.

In the proposed model, reduced substance use results via several possible final mechanisms of change, including decreased craving, enhanced self-efficacy, and increased motivation (problem recognition , desire and commitment to change). These particular mechanisms were chosen because their role in recovery from addiction is well established, and it is plausible that any of them could result from the persisting changes that are hypothesized. However, no one has yet studied the effects of hallucinogen treatment on craving, self-efficacy, and motivation in patients with addictions.

Conclusions

Evidence has converged from several lines of research in recent years to suggest that hallucinogenic drug experiences can be safely facilitated in a relatively structured supportive setting, and that such carefully tailored and purposeful experiences (as opposed to misuse or 'recreational' use) may produce persisting beneficial change. In particular, the mystical dimensions of these experiences appear to be related to positive outcomes. Persisting personality changes have been demonstrated as well. Advances in the basic science of hallucinogens provide plausible mechanisms by which hallucinogens could produce persistent change. Clinical studies with classic and non-classic hallucinogens indicate that these substances may have clinically relevant effects on depression and anxiety, and non-classic hallucinogens have shown promise in early-phase trials in drug and alcohol dependence. Several change mechanisms established in the addiction treatment literature are plausible candidate mediators of hallucinogen effects on addictive behaviour. These recent developments, taken together with the older literature, provide a convincing rationale for further research into the question of whether classic hallucinogens have clinically relevant effects on addictive behaviour, and if so whether they can be used clinically to improve treatment response among patients with addictions.

Of course this question contains within it many questions. There are many classic hallucinogens, many drugs of abuse, and many types of patients with each substance use disorder. There are also many treatment approaches that could be used with administration of hallucinogens. Among the causal change mechanisms discussed in this paper (and possibly others not even considered) different mechanisms of change could operate in different types of patients. Consequently, outcomes may vary dramatically from study to study depending on the drug, the therapeutic model, and the characteristics of the participants. We hope that the evidence reviewed in this paper and the conceptual model presented will be of use to those formulating more specific hypotheses regarding therapeutic effects of classic hallucinogens on substance use disorders, and designing and conducting studies to test these hypotheses.

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