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Classic psychedelics as therapeutics for psychiatric disorders

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I. EARLY HISTORY OF CLASSIC PSYCHEDELICS IN PSYCHIATRY

Classic psychedelics have been used by humans for many thousands of years, well before recorded history (Akers, Ruiz, Piper, & Ruck, 2011; Carod-Artal & Vázquez-Cabrera, 2006; El-Seedi, De Smet, Beck, Possnert, & Bruhn, 2005; Guerra-Doce, 2015), and among indigenous cultures with long-standing traditions of classic psychedelic use, such use typically occurs in highly ritualized, sacramental, and healing contexts (Schultes, 1969, Schultes, Hofmann, & Rätsch, 1998). Although Arthur Heffter isolated and identified mescaline as the primary psychoactive component of the peyote cactus in 1898 (Heffter, 1898), it was not until Albert Hofmann serendipitously discovered the psychoactive effects of lysergic acid diethylamide (LSD) in 1943 that Western science developed an interest in the potential clinical applications of classic psychedelics (Grinspoon & Bakalar, 1979). In many ways, this new field of research flourished, with thousands of studies evaluating the treatment of a range of mental health conditions, primarily with LSD. However, owing to a lack modern methodological rigor, most of these investigations are best understood as inconclusive, yielding pilot data—albeit promising—on safety and efficacy (Bonson, 2018). Among the most promising indications evaluated for treatment with classic psychedelics was addiction (Bowen, Soskin, & Chotlos, 1970; Chwelos, Blewett, Smith, & Hoffer, 1959; Hollister, Shelton, & Krieger, 1969; Kurland, Savage, Pahnke, Grof, & Olsson, 1971; Ludwig, Levine, Stark, & Lazar, 1969; Savage & McCabe, 1973; Tomsovic & Edwards, 1970). Indeed, a meta-analysis published in 2012 of six randomized controlled trials conducted between 1966 and 1970 found that a single dose of LSD administered in the treatment of alcohol dependence reduced alcohol misuse relative to comparison conditions as long as 6 months after treatment (Krebs & Johansen, 2012). Favorable results were also obtained in the treatment of end-of-life distress (Cohen, 1965; Kast, 1967; Kast & Collins, 1964; Kurland, 1985; Kurland, Pahnke, Unger, Savage & Goodman 1969; Kurland, Grof, Pahnke & Goodman, 1972; Pahnke, Kurland, Goodman, & Richards, 1969; Richards, 1979; Richards, Grof, Goodman & Kurland, 1972; Richards et al., 1980). Unfortunately, classic psychedelics became associated with the countercultural revolution and political tumult of the late 1960s, and by the 1970s legal proscriptions and lack of funding brought human research with these substances to an extended halt, despite the absence of a clear medical or scientific rationale (Nutt, King, & Nichols, 2013). Human classic psychedelic research began to reemerge in the 1990s (e.g., Strassman, Qualls, Uhlenhuth, & Kellner, 1994; Vollenweider et al., 1997), however, and several recent clinical studies suggest that these substances may be safe and efficacious in the treatment of a number of mental health conditions.

II. CURRENT THERAPEUTIC ROLES IN PSYCHIATRIC DISORDERS

A. Anxiety and depression

The first study of the effects of the classic psychedelic psilocybin on affect in the modern era was performed by Dr. Roland Griffiths and colleagues at Johns Hopkins

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University in 2006 (Griffiths, Richards, McCann, & Jesse, 2006). In this study, 30 normal, healthy, and hallucinogen-naive volunteers were administered either psilocybin or methylphenidate, and underwent a session that consisted of the volunteer lying in a bed wearing eye shades and listening to preselected music through headphones for 8 h (Johnson, Richards, & Griffiths, 2008). Questionnaires assessing the effects of the drugs were administered immediately after, and 2 months later. Assessments from the longer time point of 14 months were published in 2008 (Griffiths, Richards, Johnson, McCann, & Jesse, 2008). The vast majority of the volunteers had sustained positive changes in attitudes and behavior associated with the psilocybin treatment. At the 14-month follow-up, nearly 70% of volunteers rated the experience as one of the five most meaningful of their life with sustained positive well-being and attitudes toward life (Griffiths et al., 2008).

Three years later, in 2011, the first study examining the utility of a classic psychedelic to treat a psychological disorder was performed by Dr. Charles Grob at UCLA (Grob et al., 2011). After receiving regulatory approval, Grob and colleagues performed a double-blind, placebo-controlled crossover study in 12 patients with advanced cancer and reactive anxiety. Each was assigned an active placebo of niacin, or psilocybin, and underwent a treatment protocol that consisted of the patient lying in a bed wearing eye shades and listening to preselected music through headphones for 6 h. Evaluations using accepted instruments for the measure of depression and anxiety (e.g., Beck Depression Inventory, State-Trait Anxiety Inventory) were performed at 2 weeks and 6 months post session. Although no significant changes in depression and anxiety were identified between the psilocybin and niacin control groups, several trends were observed, and mean depression scores were significantly improved at 6 months compared to scores assessed at study screening, suggesting a positive therapeutic effect of psilocybin (Grob et al., 2011). Perhaps most significantly, this study established the safety and feasibility of testing psilocybin in a psychiatric patient population.

A report on the use of LSD in patients with life-threatening diseases was published by Gasser et al. in 2014 (Gasser et al., 2014). In this study, either a large dose of LSD (200 μg) or a small dose of LSD (20 μg) were administered 2 to 3 weeks apart and combined with psychotherapy sessions for 12 patients in an open-label crossover design. Assessments at 2 months and 12 months found a statistically significant improvement in anxiety associated with the higher dose of LSD (Gasser et al., 2014). As was reported by Grob and colleges (2011) for psilocybin, safety and feasibility of the use of LSD in a patient population was established. Other studies have also reported on the safety of the use of LSD in a clinical setting (Schmid et al., 2015).

Soon after these feasibility and safety studies were reported for both psilocybin and LSD, the results of additional studies were published on the use of classic psychedelics to treat anxiety and depression. The vast majority of these were on the use of psilocybin. Although psilocybin is produced by several species of mushrooms, and these mushrooms are what are taken recreationally, the psilocybin used for each of these human studies was carefully synthesized in a laboratory under controlled conditions. This is critically important as it allows for standardization of dosing and protocols for use in the clinic. A small open-label pilot study was conducted by Carhart-Harris et al. at Imperial College, UK, in 2016 demonstrating for the first time potential efficacy for treatment-resistant depression in a patient population where the depression was not linked to a life-threatening disease (Carhart-Harris et al., 2016). A high (25 mg) and low (10 mg) dose of psilocybin were administered 7 days apart with psychological support. Results indicated that psilocybin treatment was associated with antidepressant effects at 1 week and 3 months post treatment. A follow-up study found a significant reduction in depressive symptoms at 6 months (Carhart-Harris et al., 2018).

Consistent with this preliminary trial of psilocybin, several recent studies indicate that ayahuasca may be a safe and effective treatment for depression. An observational study of individuals participating in ayahuasca ceremonies ($N = 57$) found that depression significantly decreased as long as 4 weeks after the ceremonies (Uthaug et al., 2018). In an open-label pilot trial of ayahuasca among hospitalized inpatients with recurrent Major Depressive Disorder ($N = 6$), a single administration of ayahuasca (2.2 mL/kg, with 0.8 mg/mL dimethyltryptamine content) was associated with rapid reductions in depressive symptoms that endured 21 days post administration (Osório et al., 2015). These results were then replicated by the same research group in a larger sample ($N = 17$; Sanches et al., 2016). In the only randomized clinical trial of a classic psychedelic for treatment-resistant depression to date, Palhano-Fontes et al. (2018) randomly assigned participants ($N = 29$) to receive either ayahuasca (0.36 mg/kg dimethyltryptamine) or placebo. Those randomized to receive ayahuasca demonstrated significant and substantial reductions in depressive symptoms through 7-day follow-up. No serious adverse events attributable to ayahuasca administration were reported in any of these studies.

Rigorous, larger-scale, double-blind, placebo-controlled, FDA-approved phase II clinical trials were also recently conducted at Johns Hopkins University and New York University (NYU) to investigate the anxiolytic and antidepressant effects of psilocybin in patients

with life-threatening cancer. In the Johns Hopkins University study, 51 participants were randomized to a group that received a high dose (~25 mg/70 kg) first and a very low dose (~2 mg/70 kg) second, or a group that received a very low dose first followed by a high dose second. The main protocols followed were consistent with the earlier studies in healthy volunteers and involved two or more preparatory sessions prior to the first drug administration session, taking the drug and laying on a bed or couch with eye shades and listening to headphones with preselected audio for 6 h in a comfortably decorated room, followed by several postsession integrative meetings. Five weeks later patients received the second drug administration according to their group, followed by several postsession meetings. Patients were assessed by several instruments prior to the treatment, and at 1, 2, and 6 months after the drug dosing sessions. In the NYU study, a similar double-blind crossover design was followed with 29 participants taking 21 mg/70 kg psilocybin. A difference in this trial was that niacin was used as the placebo control group rather than a very low dose of psilocybin. Also, postsession assessments of depression were measured after 1 day, 6 weeks, and 6 months.

Remarkably, as demonstrated in both studies, the high-dose treatments of psilocybin resulted in rapid and sustained antidepressant and anxiolytic effects. For example, in the Johns Hopkins University study, the Hamilton Depression Rating Scale, Beck Depression Inventory, and Hamilton Anxiety Rating Scale assessments decreased each by about 80% below baseline measurements that persisted through the 6 months of monitoring. Importantly, in all of the clinical trials conducted to date, there have been no adverse reactions such as a health crisis during the treatment session or psychotic reaction. This underscores the need to conduct therapy sessions incorporating classic psychedelics within the framework of behavioral therapy and trained professionals in a clinical setting. Another important contributing factor has been the successful screening of patients to exclude those at risk for potential reactions. In each of these studies, there was a high degree of correlation between the subjective experience culminating in a "peak" or "mystical" transcendent experience and the antidepressant and anxiolytic effects, with mediator analyses indicating that such experience accounts for the efficacy of psilocybin treatment. There has been some debate in the field as to whether a transcendent experience is necessary for the antidepressant effects, or is merely a biomarker indicating that sufficient drug has been administered to produce a therapeutic effect. The nature of the subjective transcendent experience and its consequences and putative contribution to therapeutic effects are discussed later in the context of awe. Interestingly, psilocybin has been shown to produce profound and persistent antidepressant and anxiolytic effects in a rat model of treatment resistant depression (C. Nichols, unpublished data), suggesting that there may be a purely biological component as well.

B. Addiction

With regard to addiction, a single-arm, open-label pilot trial of smoking cessation treatment (N = 15) involving as many as three administrations of psilocybin (~0.29 mg/kg on the target quit date, ~0.43 mg/kg 2 weeks later, and ~0.43 mg/kg 8 weeks after the target quit date, with the option of ~0.29 mg/kg on the second and third psilocybin administrations depending on participant response) using established protocols and in conjunction with cognitive-behavioral therapy yielded biologically confirmed abstinence rates of 80% and 60% 6 months and 2.5 years after the quit date, respectively (Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014; Johnson, Garcia-Romeu & Griffiths, 2017). Although this pilot trial did not include a comparison group, abstinence rates notably outpaced those typically observed for even the most intensive of smoking cessation treatments (Hendricks, 2014). Furthermore, a single-arm, open-label pilot trial of treatment for alcohol dependence (N = 10) involving up to two administrations of psilocybin (0.3 mg/kg on the first administration and 0.4 mg/kg on the second administration, with the option of 0.3 mg/kg on the second administration depending on participant response) using established protocols and in combination with motivational enhancement therapy produced pronounced reductions in alcohol consumption sustained through 9-month follow-up (Bogenschutz et al., 2015). Finally, an observational study of ayahuasca-assisted therapy for addiction among First Nations individuals in Canada (N = 12) found that participating in up to two ayahuasca ceremonies was associated with reductions in alcohol, tobacco, and cocaine use (Thomas, Lucas, Capler, Tupper, & Martin, 2013). No serious adverse events attributable to classic psychedelic administration were reported in these investigations. Though designs employing larger samples and control conditions are needed to form more definitive conclusions, these findings suggest that further research is warranted.

III. MECHANISMS UNDERLYING THE THERAPEUTIC EFFECTS OF CLASSIC PSYCHEDELICS

A. Biological/physiological

Although major depression is a complex multifactorial disorder involving changes in central nervous

system, endocrine, and immune system functions (Chirită, Gheorman, Bondari, & Rogoveanu, 2015), dysfunction in the serotonergic system has been tightly linked to its presentation. Evidence includes decreased blood platelet levels of 5-HT, and low plasma levels of its biosynthetic precursor, L-tryptophan, in depressed individuals. Further, dietary depletion of L-tryptophan can lead to depressive-like behaviors in both humans and in animal models. Increasing 5-HT levels using medications like selective serotonin reuptake inhibitors (SSRIs) can decrease the symptoms of depression, and SSRIs as a class are currently the most effective medications used to treat major depression in the clinic.

Exactly how increasing brain 5-HT levels treats depression remains largely unknown but there are several theories. The receptor most studied in relation to major depression has been the 5-HT_{1A} receptor, which is coupled to $G_{\alpha i}$ and inhibition of adenylate cyclase. Acutely, increasing 5-HT levels in the dorsal raphe nuclei of the brain stem leads to activation of 5-HT_{1A} somatodendritic autoreceptors, a decrease in firing rates, and a decrease in cortical 5-HT release from afferents in structures like the prefrontal cortex, hippocampus, and amygdala. Chronic exposure of the 5-HT_{1A} autoreceptors in the dorsal raphe nucleus to high levels of 5-HT produced by SSRI blockade of the 5-HT transporter eventually leads to downregulation and desensitization of these receptors (Le Poul et al., 2000). Because these neurons now have fewer functional autoreceptors to respond to the negative feedback signal of 5-HT, their firing rate increases, and release of 5-HT from afferents is ultimately increased above pre-SSRI levels and remains increased for the duration of treatment. The neuroadaptation that occurs over time, involving changes in 5-HT receptor expression and function, likely underlies the antidepressant effects of SSRIs.

Another 5-HT receptor linked to major depression is the 5-HT_{2A} receptor. It is widely expressed in the brain postsynaptically on nearly every cell type including excitatory pyramidal glutamatergic neurons, inhibitory GABA interneurons, astrocytes, and glia. The 5-HT_{2A} receptor is coupled to $G_{\alpha q}$ and its activation is considered excitatory. In general, the presence of 5-HT at this receptor facilitates depolarization of neurons by either lowering the resting membrane potential, or by directly inducing depolarization, and facilitating release of the neurotransmitter associated with the cell that it is expressed on. The role of this receptor in mood and depression has not been well defined, but there are several studies linking polymorphisms of the *HTR2A* gene with depression and antidepressant medication response. In humans, SSRI treatment has been linked to a decrease in receptor density (Muguruza et al., 2014), and in animal models blockade of the receptor has been shown to potentiate the antidepressant effects of SSRIs (Quesseveur et al., 2013). Therefore, reduction in 5-HT_{2A} receptor function, likely due to desensitization and downregulation of enhanced 5-HT levels, has been suggested as a mechanism underlying SSRI efficacy to treat depression.

How then might classic psychedelics produce antidepressant effects in humans? In animal models and in humans, classic psychedelics can acutely produce activation of the hypothalamic–pituitary–adrenal (HPA) axis and anxiety. It is not until the behavioral effects have subsided that subjects report improved affect. Remarkably, the improved mood and antidepressive effects can be long-lasting and those from a single treatment can last at least several months. The primary classic psychedelic used in clinical trials, psilocybin, is an agonist at both 5-HT_{2A} and 5-HT_{1A} receptors, with its primary psychoactive effects mediated by activation of 5-HT_{2A} receptors. It is highly unlikely that its antidepressant effects are mediated by molecular mechanisms similar to those of SSRIs, which require long term neuroadaptation to occur. There are likely two primary components: a psychological component and a biological component that together interact to produce its profound effects. The psychological component will be discussed in a later section. At the biological level there are likely several mechanisms at play.

Classic psychedelics directly activate a small percentage of excitatory neurons, the Trigger Population, which then leads to activation of small populations of inhibitory interneurons, astrocytes, and glia cells, with an overall activation of neural circuitry (Martin & Nichols, 2016). Significantly, the nature of how these cells and circuits are activated is different between different regions of the brain. These molecular and cellular changes manifest at the systems level to likely desynchronize neuronal activity and destabilize the Default Mode Network (DMN), and produce a hyperconnectivity between brain regions (Carhart-Harris et al., 2017). Differential changes in connectivity likely result from differential cellular and molecular responses to classic psychedelics between brain regions. One theory proposes that network connectivity is abnormal in the depressed state, and that after the desynchronization and hyperconnectivity produced by classic psychedelics, the DMN resets to a normal nondepressed state of synchronicity and connectivity (Carhart-Harris et al., 2017). A modification of this theory to address the long lasting effects after a single treatment involves the anti-inflammatory effects of classic psychedelics. In this scenario, the classic psychedelic treatment will not only reset the DMN, but also reduce and eliminate comorbid neuroinflammation, preventing the brain from relapsing to an abnormal state again due to persistent neuroinflammation. Another factor that may contribute to antidepressant effects is the ability of 5-HT_{2A}

(Nichols et al., 2017) receptor agonists to rapidly induce dendritic spine growth and density, similar to what has been observed for ketamine, which can also elicit significant and rapid antidepressant effects. The effects of ketamine, however, are not long-lasting and typically subside after a few weeks. This may be due to the lack of anti-inflammatory properties associated with ketamine.

B. Drug abuse

Mesolimbic and basal ganglia pathways form the foundation of the brain's reward circuitry, and their roles in addiction have been clearly demonstrated by a variety of methods that include lesioning in whole animals, behavioral pharmacology, and sophisticated imaging techniques (Koob & Volkow, 2009). Although dopamine (DA) is a crucial neurotransmitter involved in the response to stimulant drugs, 5-HT has been found to also be important in mammalian response both as a dopaminergic modulator and by direct action (Alex & Pehek, 2007). There have been many studies exploring the role of individual 5-HT receptors in addiction, with a focus on the 5-HT_2 and 5-HT_{1A} receptor families (Bubar & Cunningham, 2008; Filip, Alenina, Bader, & Przegaliński, 2010; Muller, Carey, Huston, & de Souza Silva, 2007; Müller & Homberg, 2015). 5-$HT_{2A/C}$ receptors are expressed in key areas of the brain that mediate reward and addiction including the ventral tegmental area (VTA) and nucleus accumbens (NAc), and modulate DA levels. Interestingly, 5-HT_{2A} and 5-HT_{2C} receptors functionally oppose one another, with activation of 5-HT_{2A} receptors increasing DA release and 5-HT_{2C} receptors decreasing DA release. The ability of 5-HT_{2A} receptor stimulation to increase DA levels likely results from their expression on VTA dopaminergic neurons, where their stimulation can directly lead to DA release, and their expression on cortical glutamatergic neurons, where their stimulation facilitates excitatory glutamatergic input to the VTA leading to an indirect enhancement of DA release. Although inhibitory GABAergic interneurons in the VTA and PFC express both, 5-HT_{2A} and 5-HT_{2C} receptors, expression of 5-HT_{2C} receptors on these cells is significantly higher. Therefore, selective activation of these receptors produces GABA-mediated inhibition of dopaminergic release from VTA neurons, and of glutamatergic inputs from the prefrontal cortex (PFC).

With respect to alcohol use, against which psilocybin has demonstrated clinical efficacy as described above, the amygdala is believed to substantially contribute to the development and maintenance of dependence (Aznar & Klein, 2013; Gilpin & Roberto, 2012; Koob & Volkow, 2009). One of the major changes induced by alcohol addiction is a facilitation of GABAergic neurotransmission in the central amygdala (CeA) that results in disinhibition of output signals to other structures like the hypothalamus and locus coeruleus. 5-HT_{2A} receptors are expressed on glutamatergic pyramidal neurons and GABAergic interneurons of the basolateral amygdala (BLA), as well as on glutamatergic neurons of the vmPFC, which send projections to the amygdala and modulate its function and influence emotions. Therefore, 5-HT_{2A} receptor function in the amygdala and ventro-medial PFC may have a critical role in the etiology of alcohol dependence.

Similar to the potential therapeutic effects of classic psychedelics to treat depression, there are likely psychological and physiological components to the efficacy of classic psychedelics to treat addiction. Unlike with depression, where there is currently no evidence definitively establishing a physiological component, there is data from animal models demonstrating that classic psychedelics have efficacy to block drug seeking behaviors ranging from cocaine self-administration to alcohol preference (Maurel, De Vry, & Schreiber, 1999). The simplest explanation is that classic psychedelics, which nonselectively activate both 5-HT_{2A} and 5-HT_{2C} receptors, have therapeutic effects by activating 5-HT_{2C} receptors and that this activity overcomes the effects of 5-HT_{2A} receptor activation to produce an overall net decrease of DA release in the mesolimbic system. A reduction in the dopaminergic response would be predicted to reduce craving and drug-seeking behavior. This is the predicted mechanism of 5-HT_{2C} selective agonists like lorcaserin for decreasing drug craving. This is not the case, however, with the classic psychedelic 2,5-Dimethoxy-4-iodoamphetamine(DOI), which when given systemically leads to a dramatic increase in VTA DA levels (Pehek & Hernan, 2015), despite activation of both receptor isoforms. Perhaps the ability of psilocybin to activate 5-HT_{1A} receptors in addition to 5-HT_2 receptors is significant for therapeutic efficacy? Data show that psilocin, the active metabolite of psilocybin, does not alter DA levels in the VTA, but increases levels in the NAc (Sakashita et al., 2015). Together, these data indicate that the likely therapeutic mechanism of action does not involve classic psychedelic-mediated reductions in mesolimbic DA levels. Nevertheless, preclinical studies have shown that classic psychedelics like psilocybin and DOI can reduce alcohol consumption in rat models, without altering taste perception. Potentially relevant to this is that 5-HT_{2A} receptor activation has been demonstrated to dramatically enhance the process of fear memory extinction (Catlow, Song, Paredes, Kirstein, & Sanchez-Ramos, 2013).

With regard to nicotine dependence, DA in the mesolimbic system is also known to play a key role, as is the amygdala. Studies with rodents have indicated that, as with other stimulants, treatment with selective 5-HT_{2C}

agonists reduces the effects of nicotine (Zaniewska, McCreary, Przegaliński, & Filip, 2007). Interestingly, activation of 5-HT_{2A} receptors also blocks the effects of nicotine (Zaniewska et al., 2007). In another study, activation of 5-HT_{1A} receptors had no effect on nicotine responses (Batman, Munzar, & Beardsley, 2004), suggesting that the therapeutic effect of psilocybin to treat nicotine dependence likely does not involve its activation of these receptors. In summary, the mechanisms underlying the ability of classic psychedelics to treat alcohol and nicotine dependence likely primarily involve 5-HT_{2A} receptor activation, with minimal contribution from other receptors like 5-HT_{2C} and 5-HT_{1A}. The role of 5-HT_{2A} receptor activation in these processes is likely complex, and remains to be elucidated at the cellular and molecular level.

The anti-inflammatory effects of classic psychedelics (Flanagan & Nichols, 2018) may also contribute to their efficacy to treat drug addiction at the cellular level. Neuroinflammation has been found to be associated with aspects of drug addiction including cocaine seeking (Brown et al., 2018), opioid dependence (Catherine & Cahill, 2017), and alcohol use disorder (Crews, Walter, Coleman, & Vetreno, 2017). Conversely, nicotine has been shown to impair immune responses within the CNS, and whereas nicotine itself has inhibitory effects on immune cell activation, other components of tobacco smoke likely produce the bulk of immune cell dysfunction in smokers (Brody et al., 2017; Nizri et al., 2009).

C. Awe

At the psychological level, Hendricks (2018) recently proposed that the discrete emotion awe might be responsible for effects of classic psychedelics. As expounded by Hendricks, awe is experienced whenever humans encounter stimuli so vast and novel that they must alter their understanding of reality. Nature, religious/spiritual practices, and music are common elicitors of awe. At the core of awe's acute effects is the *small self*, which involves attention being directed away from the self, feelings of unity with others and/or the environment, and diminishment of individualistic tendencies. From the perspective of the social functional approach to emotions in which emotions aid in the coordination of social interaction, awe is believed to be the quintessential binding emotion that drives social integration and cooperation, which are crucial to evolutionary success. According to Hendricks, classic psychedelics may ultimately produce profound awe. Thus, for those suffering from addiction marked by considerable disruption in social functioning, an experience that highlights the discrepancy between the hedonic pursuit of drug rewards and the eudaimonic pursuit of a cause greater than self (e.g., family) may provide the motivation for sustained sobriety. For those suffering from end-of-life distress, depression, or other conditions characterized by maladaptive, self-directed rumination, attention directed away from the self and toward the transcendent may account for improvements in anxiety and mood. Of course, these effects may be reflected in the biological/physiological mechanisms mentioned above. These are hypotheses to be tested by future research.

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