Chapter 78

Lysergic Acid Diethylamide and Mystical Experiences

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Abbreviations

2CI-NBOMe 2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl) methyl]ethanamine
5-HT$_2$ 5-Hydroxytryptamine (serotonin) receptor subtype
D$_2$ Dopamine receptor subtype
DMT Dimethyltryptamine
DOM Dimethoxymethylamphetamine
HPPD Hallucinogen persisting perceptual disorder
LSD Lysergic acid diethylamide
MAO Monoamine oxidase
MDMA Methylenedioxymethamphetamine
NDE Near-death experience
PTSD Posttraumatic stress disorder
REM Rapid eye movement

INTRODUCTION: LYSERGIC ACID DIETHYLAMIDE IN THE CONTEXT OF OTHER PSYCHEDELIC AGENTS

The term psychedelic ("mind-manifesting") was coined by British psychiatrist Humphry Osmond in 1956 to refer to a unique class of mind-altering chemicals with distinctive effects that set them apart from other drugs with hallucinogenic properties. Some psychedelics come from natural sources that have been traditionally featured in religious, ritual, and healing practices of indigenous cultures of the Americas (Anderson, 1980; Hofmann, 1983; Salak, 2007; Smith, 2000); such drugs include mescaline (from peyote and San Pedro cacti), psilocybin and psilocin (from *Psilocybe* mushrooms), and dimethyltryptamine or DMT (from the leaves of *Psychotria viridis*). Many other psychedelics have partly or wholly synthetic origins. The most potent psychedelic agent yet discovered is the semisynthetic ergot derivative lysergic acid diethylamide (LSD), which has distinctive effects at the microscopic dose of 25 µg; a typical psychedelic dose ranges from 50 to 200 µg. There are also a number of purely synthetic psychedelics, many of which are chemically related to both amphetamine and mescaline (Shulgin & Shulgin, 1991). One of the most potent of these is dimethoxymethylamphetamine, or DOM, which was known as "STP" when introduced to the hippie subculture of San Francisco in the late 1960s. More familiar today is methylenedioxymethamphetamine (MDMA, ecstasy), which has only mild or partial psychedelic effects as opposed to full psychedelics such as LSD, psilocybin, and mescaline; MDMA is thus sometimes described as an "entactogen," meaning "touch within" (Bravo, 2001; Smith, 2000), as opposed to full psychedelics or "entheogens," meaning "God within." A newer, extremely potent synthetic psychedelic, 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl] ethanamine (2CI-NBOMe, or "N-Bomb"), was invented in 2003 and is useful as a laboratory tool to map brain serotonin receptors (Ettrup et al., 2010). The threshold dose is several hundred micrograms, making this psychedelic second in potency only to LSD. Media reports indicate that 2CI-NBOMe has been sold to drug users on pieces of blotter paper, like LSD, and often misrepresented as the latter drug. Unfortunately 2CI-NBOMe has a much lower therapeutic index than LSD, hence several highly publicized deaths appear to have been caused by this drug (e.g., Hastings, 2013; Poklis et al., 2014) and, in some cases, possibly misattributed to LSD. Some of the deaths resulted from drug-induced seizures, whereas in other cases the individuals killed themselves accidentally or purposefully in a drug-induced psychotic or delirious state. By contrast, fatal reactions are extremely uncommon with the "classic" psychedelics LSD, psilocybin, and mescaline.

PHARMACOKINETIC ASPECTS OF LSD AND OTHER PSYCHEDELICS

Psychedelics differ widely in terms of properties such as potency, route of administration, side effects, and duration of action. DMT is the shortest-acting psychedelic, with effects lasting less than half an hour when injected, snorted, or smoked. By contrast, the psychedelic experiences induced by a full dose of LSD or mescaline can last 12–14 h or more, whereas psilocybin and psilocin typically last 4–6 h. A 100-µg dose of LSD is considered roughly equivalent in effect to a 300-mg dose of mescaline, showing the 3000-fold difference in potency between these two drugs. LSD, mescaline, and psilocybin are highly effective orally, whereas DMT is normally broken down by the enzyme monoamine oxidase (MAO) in the gut and liver and thus must be administered via nonoral routes (usually by smoking or sniffing) to have any effect if taken on its own. However, in the indigenous Amazonian drink ayahuasca, DMT from the leaves of *P. viridis* is mixed with the MAO inhibiter harmaline from

the yage vine; this allows DMT to take effect by the oral route because MAO-mediated breakdown of DMT is blocked, allowing absorption into the bloodstream. Indigenous tribes of the Amazon rain forest thus effectively discovered that DMT can be rendered orally active if combined with an MAO inhibiter (though of course they do not explain it in such terms!), long before the advent of modern biochemistry—presumably through experimentation with different combinations of plant extracts.

THE PSYCHEDELIC TRIP

Although different psychedelics reportedly vary to some extent in the characteristics of the effects they produce (e.g., psilocybin is said to be more "visual," whereas LSD is said to be more "intense"; Grinspoon & Bakalar, 1979; Leary, 1968), all full psychedelics will, if taken in sufficient doses, produce extreme alterations of consciousness. The resulting experience is colloquially referred to as a "trip." Brilliantly multicolored visions typically unfold in the mind's eye; time is dramatically dilated so that minutes may seem like hours, or perhaps even "eternity"; there is dissolution of ego boundaries; the individual becomes emotionally labile and hypersensitive to both internal and external stimuli; and revelations of a transpersonal or spiritual nature may be experienced (as discussed later). In some instances intense hallucinatory experiences, fear of impending ego-death, and negative emotions can overwhelm the user, leading to a panic attack or acute psychotic reaction called a "bad trip." The first appearance of LSD in a Hollywood movie emphasized this dark side of psychedelics; the movie was the 1959 camp classic *The Tingler*, starring Vincent Price as a researcher experimenting with LSD to induce acute terror. Adverse psychological reactions are more likely when the drug is taken casually, without adequate preparation, in high doses, and/or in an uncontrolled or unfamiliar setting (Cohen, 1970; Grinspoon & Bakalar, 1979; Hofmann, 1983; Johnson, Richards, & Griffiths, 2008; Stafford, 1983).

RISKS OF PSYCHEDELIC DRUG USE

The classic psychedelics are very safe in a physical sense, meaning a fatal overdose is extremely unlikely. LSD and psilocybin have very high therapeutic indices such that the lethal dose may be hundreds of times the effective psychedelic dose. Psychedelics are not addictive; even enthusiastic proponents of psychedelics take them only occasionally because of the intensity of the effects, the felt need for a recovery period, and the rapid onset of short-term tolerance. Interestingly, *Homo sapiens* appears to be the only species that will voluntarily take a psychedelic drug such as LSD or psilocybin after experiencing the effects previously. Although laboratory animals such as rats and monkeys will readily and repetitively self-administer many other drugs used recreationally by humans, including cocaine, nicotine, amphetamines, heroin, and alcohol, they apparently find LSD aversive (Verster, Brady, Galanter, & Conrod, 2012). When dosed with LSD or another full psychedelic by a researcher, laboratory animals such as cats, monkeys, and chimpanzees often show signs of fear. Thus in contrast to habit-forming drugs, which are positive reinforcers in many species, full psychedelics appear to have aversive, anxiogenic effects in nonhumans.

The chief hazards of psychedelic use are psychological in nature (Cohen, 1970; Hofmann, 1983; Johnson et al., 2008). In high doses their effects can be extremely intense, unpredictable, and uncontrollable. Bad trips can cause lasting symptoms of posttraumatic stress disorder (PTSD), a syndrome characterized by panic attacks and flashbacks, in susceptible individuals. In rare cases, users have committed suicide during or after bad trips. Enjoying good psychological health and having experienced fulfilling trips previously does not mean a bad trip will never occur; neuroscientist and writer Sam Harris (2011) has described how, after several highly rewarding LSD experiences, he was utterly unprepared for the horrors of an unexpected bad trip on a high dose taken in an uncontrolled setting outdoors. Those who have conducted research on the effects of psychedelics in humans concur that when the drug is taken in a controlled setting by a psychologically stable individual, with a sober and trustworthy "sitter" on hand to assist the user if needed, and only for a serious (e.g., spiritual or autognostic) purpose following intensive preparation, the likelihood of bad trips can be minimized (Johnson et al., 2008; Stafford, 1983).

Today, low doses of LSD (typically around 50 μg) are sometimes taken recreationally at concerts and dance clubs to enhance sensations (Hidalgo, 2009; Laing & Siegel, 2003), but in the 1960s many of those who experimented with psychedelics, including well-known artists, philosophers, writers, and musicians, took far higher doses (200+ μg) in a quest for self-knowledge and spiritual enlightenment. Unfortunately a few did not return fully intact from their inner journeys, with the list of claimed "acid casualties" of the 1960s famously including Brian Wilson of the Beach Boys (see Petrides, 2011) and Syd Barrett of Pink Floyd (see Schaffner, 2005). By contrast the actor Cary Grant (as cited in Beauchamp & Balaban, 2010), poet Alan Ginsberg (as cited in Stafford, 1983), philosopher Alan Watts (1965), writer Aldous Huxley (1956), and Beatle George Harrison (as cited in Greene, 2006) were among those who felt that their LSD experiences had changed them for the better by affording them profound insights into themselves and the nature of reality. Psychedelic experiences with positive outcomes can be described as "integrative" in that they promote acceptance and a sense of meaning and coherence in the user's life, in contrast to the "disintegrative" experiences and maladaptive aftereffects of bad trips. But in some cases even a disintegrative bad trip may have the positive "side effect" of promoting compassion for those who, through no fault of their own, find themselves the victims of brain chemistry and subjective reality gone awry, as in schizophrenia. Indeed, one of the rationales for psychiatrists taking LSD in the 1950s was to help them gain insight into the distorted realities of psychotic patients, although it was eventually recognized that the psychedelic states induced by LSD do not resemble endogenous psychoses (Grinspoon & Bakalar, 1979).

PSYCHEDELIC MYSTICAL EXPERIENCES

Perhaps the most fascinating and controversial aspect of psychedelic drugs concerns reports from many users—among them prominent scientists, psychiatrists, and intellectuals—of life-changing, transcendental, or mystical/religious experiences induced or facilitated by these drugs, especially (though not exclusively) LSD (Griffiths, Richards, McCann, & Jesse, 2006; Harris, 2011; Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004; Hofmann, 1983; Horgan, 2003; Leary, 1965; Lerner & Lyvers, 2006; Lyvers & Meester, 2012; MacLean, Johnson, & Griffiths, 2011; Maslow, 1964; Masters & Houston, 1966; Pahnke, 1963, 1969; Pahnke &

Richards, 1966; Smith, 2000; Stevens, 1998; Watts, 1965). Mystical experiences have been reported in every major religious tradition; such reports share in common with accounts from LSD users the claim of having transcended the individual self or ego to face Ultimate Reality, God, the ineffable Ground of Being, the True Self (Grinspoon & Bakalar, 1979; Horgan, 2003; James, 1902/1961; Spilka, Hood, & Gorsuch, 1985; Suzuki, 1957/2002; Watts, 1965). This tends to occur independent of visionary or hallucinatory phenomena, which can vary quite widely in frequency and content across individuals and religious traditions. Profound mystical experiences can have a lasting impact; Apple founder Steve Jobs considered his LSD trip to be one of the most important experiences of his life (as cited in Isaacson, 2011), and there are far too many such accounts by highly intelligent, scientifically minded people for this aspect of psychedelic experiences to be airily dismissed as mere hallucination or delusion. In a 2006 study by Griffiths et al. highly educated, drug-naïve volunteers were administered the psychedelic drug psilocybin in a double-blind, active placebo design; like Steve Jobs, most of those given a full psychedelic dose rated the resulting mystical experience as one of the most important and influential events of their lives, with a lasting positive impact on personality suggested by long-term follow-up (MacLean et al., 2011). The Griffiths et al. study was a replication and extension of earlier work at Harvard by Pahnke and colleagues, who in 1962 recruited Boston divinity students as subjects; most divinity students who were given psilocybin reported mystical experiences (although one apparently had a psychotic reaction), compared to none in the active placebo group. A 25-year follow-up (Doblin, 1991) confirmed the lasting subjective positive impact of psilocybin-induced mystical experiences in Pahnke's former subjects. Such life-altering effects would seem to demand a scientific explanation, but as yet science has not been able to provide a convincing explanation as to how and why certain patterns of physiological brain activity are accompanied by subjective experiences at all (Chalmers, 1996), much less mystical ones. Arguably, until such profound issues are resolved—which may never happen given human cognitive limitations (McGinn, 1991)—the mystical experiences induced or facilitated by psychedelics may never be fully explained by science, despite the progress to date in our understanding of how these drugs affect the brain.

MECHANISMS OF LSD ACTION

Research on the pharmacodynamics of psychedelic drugs has revealed that the classic psychedelics have structural similarities to the ubiquitous neurotransmitter serotonin (see Figure 1) and are direct serotonin agonists, meaning they bind to and activate serotonin receptors, particularly the most common type of serotonin (or 5-HT) receptor, the excitatory postsynaptic 5-HT_2 receptor. LSD additionally directly activates D_2 dopamine receptors, which may pertain to differences reported between the effects of LSD and those of other psychedelics. In any case activation of 5-HT_2 receptors by psychedelic drugs, including of course LSD, triggers a dramatic increase in release of the excitatory neurotransmitter glutamate in cortical, thalamic, and limbic regions (Hintzen & Passie, 2010; Vollenweider & Kometer, 2010), as represented schematically in Figure 2. The result is hyperactivation of the prefrontal cortex, or hyperfrontality, most prominently in the right hemisphere (Hasler et al., 2004; Vollenweider et al., 1997), the visuospatial, emotional, nonverbal side of the brain. Contrary to the outdated "waking dream" interpretation of psychedelic effects postulated in the 1970s (Jacobs & Trulson, 1979), physiologically the states induced by psychedelics are not at all akin to dream states but rather more resemble extremely amplified waking states, as serotonergic receptor activation is normally highest during waking and entirely ceases during rapid eye movement, or dream, sleep (Portas, Bjorvatn, & Ursin, 2000). The serotonin agonist action of psychedelics also results in strong sympathomimetic effects such as dilated pupils, muscle tremors, and increased heart rate and blood pressure, owing to serotonergic receptor-mediated

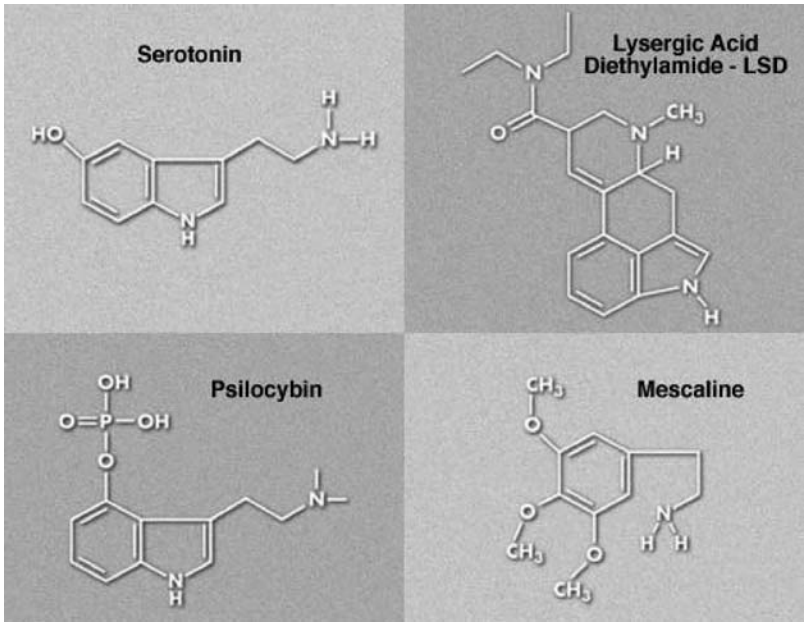

FIGURE 1 Structures of serotonin, LSD, psilocybin, and mescaline.

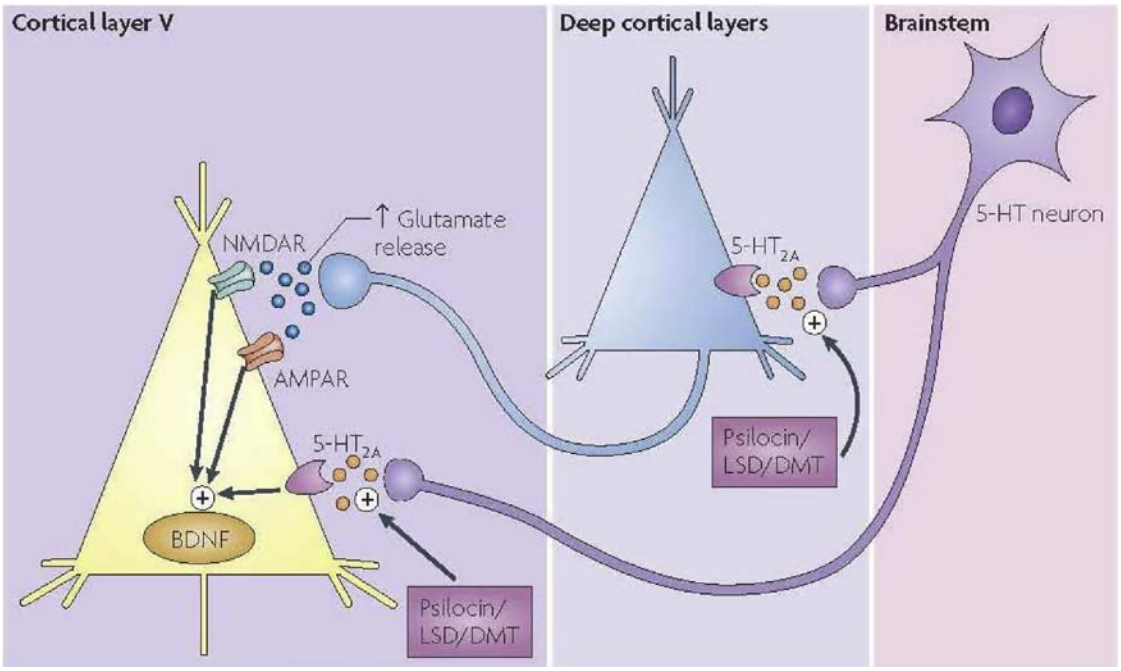

FIGURE 2 Model of psychedelic drug action via activation of 5-HT_2 receptors and induced release of glutamate in the cortex. NMDAR, *N*-methyl-D-aspartate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; LSD, lysergic acid diethylamide; DMT, dimethyltryptamine. *Reprinted by permission from Vollenweider and Kometer (2010), © 2010, Macmillan Publishers Ltd.*

activation of the brainstem locus coeruleus, which regulates the sympathetic nervous system. But current research points to excessive glutamate release in higher brain regions, particularly the prefrontal cortex, in response to strong stimulation of 5-HT_2 receptors as the likely brain basis of the intense subjective effects of psychedelic drugs, including perhaps mystical experiences.

Interestingly, research on near-death experiences has supported a glutamate overflow theory of this type of mystical experience as well (Borjigin et al., 2013; Jansen, 1997; Parnia, 2013), and a serotonergic mechanism of increased prefrontal cortical theta activity induced by Zen meditation has been suggested (Takahashi et al., 2005). Thus it appears possible that the mystical experiences sometimes reported following ingestion of a high dose of LSD and those reported by Zen Buddhist meditators, as well as by a significant minority of individuals who have clinically died and been resuscitated, may all have a common physical correlate in similar alterations in brain activity. If confirmed this would pertain to the controversy over whether a mystical experience induced or facilitated by LSD (or other psychedelics) is "genuine"; one may be tempted to argue that, from a scientific perspective, if similar alterations in brain activity are common to each, then a psychedelic mystical experience may be just as "genuine" as mystical experiences reported following clinical death and resuscitation or following an intensive period of Zen meditation aimed at attaining *kensho* (enlightenment). Furthermore the related question of which mystical experiences are "real" in terms of offering valid insights into the nature of self and reality naturally leads to other, perhaps (for some) uncomfortable questions about the fundamental nature of everyday subjective reality and its dependence on normal waking brain chemistry—a common insight reported by even nonscientifically oriented psychedelic drug users who have seen their own everyday reality rather emphatically shaken up by a potent brain-altering chemical agent such as LSD.

DISCOVERY OF THE PSYCHEDELIC PROPERTIES OF LSD

Arguably no mind-altering drug has a more colorful history than LSD; hence only a brief synopsis of some of the highlights can be presented here. In April 1943 Sandoz chemist Albert Hofmann (Figure 3) was handling a vial containing a relatively new compound labeled LSD-25, with unknown properties. Later that day he experienced a strange altered state of consciousness. Suspecting that LSD was the cause—presumably a miniscule amount had accidentally absorbed through his skin—Hofmann decided to test the drug on himself starting with what he thought would be a small and safe oral dose, only ¼ of a milligram (250 μg). This is actually a very large dose of LSD, but at the time Hofmann did not suspect that any psychoactive drug could possibly be that potent. Hofmann's trip on 250 μg was overwhelmingly intense to the point at which he thought he was dying and had his family call a physician, who found nothing physically wrong with him. Unprepared as Hofmann was for the mind-shaking effects of a full psychedelic dose of LSD, Hofmann had a terrifying experience, which he later described as "demonic" (Hofmann, 1983) but which eventually subsided into a fantastic hallucinatory display as the peak of the drug effect passed. Hofmann recovered and a period of scientific research on LSD began.

LSD AND A "MODEL PSYCHOSIS"

With the discovery of the powerful psychedelic effects of LSD, the initial consensus was that LSD induced a model psychosis—a temporary drug-induced schizophrenia. LSD thus inspired the "endogenous psychotogen" theory of schizophrenia, which postulated that the disease was caused by an unidentified LSD-like chemical produced in the patient's body via an error of metabolism. Eventually, however, psychedelic experiences were recognized as

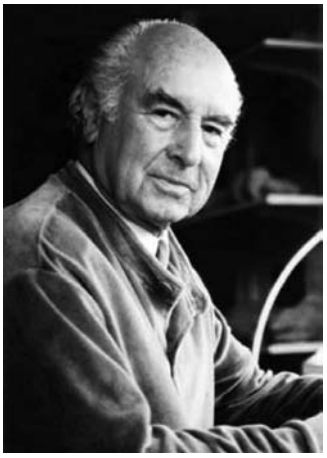

FIGURE 3 Albert Hofmann, discoverer of the psychedelic properties of LSD. *nndb.com*.

FIGURE 4 Actor and LSD psychotherapy patient Cary Grant. *carygrant.net*.

having very different features from the experiences of a schizophrenic undergoing an acute psychotic episode, and even schizophrenics could distinguish the effects of LSD from their own endogenous psychotic states (see Grinspoon & Bakalar, 1979, pp. 245–253). Nevertheless research has brought renewed attention to the involvement of serotonin systems in both endogenous and LSD-induced hallucinatory states (Geyer & Vollenweider, 2008).

LSD AS A CHEMICAL CATALYST FOR CHANGE

In October 1955 psychiatrist Sidney Cohen (1970) took LSD expecting a frightening psychotic state like that of his schizophrenic patients, but instead soon found himself in a peaceful realm of "eternal truth." As a result of the increasing number of such accounts the therapeutic potential of LSD was investigated. LSD came to be regarded by some as the key that could unlock the secrets of the unconscious mind. In the 1950s and into the 1960s LSD was legally administered to thousands of patients in the United States, most often in the context of two types of psychotherapy: psycholytic therapy and psychedelic therapy (see Grinspoon & Bakalar, 1979, Chapter 6). In psycholytic ("mind-loosening") therapy, relatively small doses of LSD (50–150 µg) were administered in the context of Freudian or Jungian psychotherapy to facilitate the emergence of repressed material. The most famous psycholytic therapy patient and proponent was the actor Cary Grant (Figure 4) (Beauchamp & Balaban, 2010). However, given the unpredictability of LSD's effects even at relatively lower psycholytic doses, the milder quasi-psychedelic or "entactogenic" drug MDMA has been suggested to be a better candidate as a psycholytic therapy agent (Naranjo, 2001).

Psycholytic therapy originally involved the administration of small doses of LSD over many therapy sessions. In psychedelic therapy, by contrast, a large dose of LSD (e.g., 200+ µg) was administered on only one or two occasions with the goal of inducing a life-changing mystical experience. This approach was used with some success to treat chronic alcoholism and to prepare terminal cancer patients for their impending death. Bill W., the founder of Alcoholics Anonymous, became an early advocate of psychedelic therapy for alcoholism after experimenting with LSD himself (as cited in Novak, 1997). He regarded LSD as capable of shattering the ferocious ego of the alcoholic, making him or her hit "rock bottom" and awakening an awareness of a higher power—necessary steps toward a life of abstinence from alcohol. A 2012 meta-analysis of psychedelic therapy for alcoholism (Krebs & Johansen, 2012) concluded that a single high dose of LSD compared favorably in treatment outcome to the currently approved daily medications for alcoholism naltrexone, acamprosate, and disulfiram (see Table 1), with 59% of LSD patients showing significant improvement at follow-up versus 38% of controls. This result is especially striking given that half of the clinical trials examined did not prepare their alcoholic patients for the intense effects of LSD, making bad trips more likely. Krebs and Johansen concluded that further clinical trials of LSD psychedelic therapy for alcoholism are warranted following the lengthy hiatus in such work since the late 1960s, when research on the potential therapeutic benefits of LSD was curtailed owing to legal and cultural factors (as described below).

LSD was also investigated for military purposes in the 1950s and 1960s (Lee & Schlain, 1992). During the Cold War, the CIA was interested in LSD as both a mind control agent and a potential "humane" chemical weapon. In the early 1960s, unscrupulous CIA agents surreptitiously administered LSD to colleagues and civilians to test their reactions; at least one suicide resulted from this. LSD has also been used as a mind control agent by psychopathic criminals to help them "brainwash" their cult followers; the most notorious examples are Charles Manson, whose followers committed the gruesome Tate–LaBianca murders in 1969, and Shoko Asahara, whose followers committed mass murder by releasing sarin nerve gas on Tokyo subways in 1995. But the decline in scientific and psychiatric interest in LSD had less to do with high-profile crimes than with the popularization of LSD in the 1960s as a mystical tool for the masses that had the potential to transform society, and the political and legal backlash against this.

LSD, MYSTICISM, AND SOCIETY

The cultural impact of LSD in the 1960s cannot be underestimated. Widespread self-experimentation by artists, writers, musicians, and intellectuals inspired psychedelic styles in art, cinema, literature, and music, in addition to popularizing the concept of a transformative mystical experience that was potentially accessible to everyone by means of a chemical catalyst—as opposed to many years of

TABLE 1 Meta-Analysis of Randomized Controlled Clinical Trials of Single-Dose LSD versus Daily Naltrexone, Acamprosate, and Disulfiram for Treatment of Alcoholism

	Benefit Difference							
	LSD, Single Dose		Naltrexone, Daily		Acamprosate, Daily		Disulfiram, Daily	
Outcome	(95% CI)	NNT	(95% CI)	NNT	(95% CI)	NNT	(95% CI)	NNT
Improvement in alcohol misuse or return to heavy drinking	16% (8%, 25%)	6	11% (7%, 15%)	9	1% (–2%, 5%)	100	Not reported	
Maintained abstinence or return to any drinking	15% (4%, 25%)	7	3% (1%, 6%)	33	11% (7%, 15%)	9	11% (–1%, 22%)	9

LSD outcomes are at first follow-up after single dose and are compared to no drug or active placebo. Naltrexone and acamprosate outcomes are during daily drug treatment and are compared to placebo. Disulfiram outcomes are during daily unsupervised drug treatment and are compared to other or no treatment. Data on naltrexone, acamprosate, and disulfiram extracted from published meta-analyses (Rösner et al., 2010a, 2010b; Krampe and Ehrenreich, 2010). Pooled benefit differences calculated using a random-effects, inverse variance method. Benefit difference = % patients with beneficial outcome in experimental - % patients with beneficial outcome in control. Number needed to treat (NNT) = 1/(benefit difference).
CI, confidence interval.

meditation or other rigorous spiritual practices that offered the hope of, but did not guarantee, eventual union with the divine (the inconvenient fact that LSD, too, did not guarantee union with the divine appeared to escape notice). The most influential promoter of LSD as a mystical tool for the masses was Harvard psychology professor Timothy Leary (Figure 5), who in 1960 had been introduced to the sacred *Psilocybe* mushrooms while holidaying in Mexico. Overwhelmed by the resulting (as he described it) "religious experience," Leary concluded that psilocybin was the psychological and spiritual equivalent of a microscope or telescope, a revolutionary new instrument, which he dedicated himself to exploring further (Leary, 1968, 1983). However, during the following year in Boston he was introduced to the far more powerful drug LSD, which he came to regard as "the sacrament," with himself the devoted "high priest" (Leary, 1968). Leary's mission, encapsulated in his catchy slogan "Turn On, Tune In, Drop Out," was to get as many people as possible to take LSD to change society from within. Leary's adventures and misadventures with LSD, various cultural icons, and the legal system are entertainingly recounted in his two autobiographies (Leary, 1968, 1983). Leary was a charismatic, messianic, and divisive figure, who was more responsible than anyone else for popularizing LSD (inspiring popular songs by the Beatles and the Who, among others); in doing so he inevitably aroused the wrath of the political and legal establishments—which responded by making the drug strictly illegal for any purpose, bringing scientific and medical research on LSD to a grinding halt, and by arresting and imprisoning Leary. His advocacy of LSD for the masses was considered extremely irresponsible by those who acknowledged the positive potentials of LSD but who also recognized the potential dangers of uncontrolled use (Cohen, 1970; Hofmann, 1983).

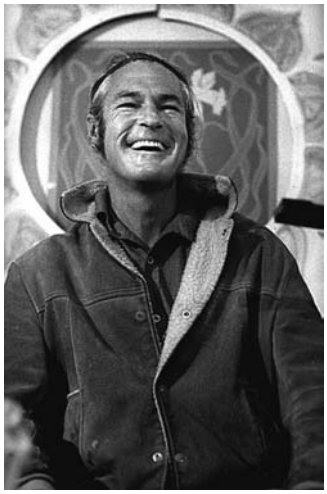

FIGURE 5 Psychologist Timothy Leary, self-styled "high priest" of LSD. *leary.taolodge.com*.

LSD AND MYSTICAL EXPERIENCES IN THE TWENTY-FIRST CENTURY

Despite cultural shifts and a dramatic reduction in unit doses of LSD sold on the black market today in comparison to the large doses distributed in the 1960s, the drug still appears to be capable of inducing or facilitating mystical experiences in a substantial proportion of illicit users. As of February 6, 2014, the drug information website erowid.org had posted 1309 personal accounts of LSD experiences under 16 categories (including 162 "bad trips" and 78 "trip disasters"); there were 143 accounts posted under "mystical experiences" and 238 accounts posted under the similar category "glowing experiences," and many of the accounts in the other categories (e.g., "General") featured strong mystical or spiritual aspects. In a 2012 study Lyvers and Meester recruited 337 drug users from the Internet to complete an online survey; information about typical dose of each drug used was obtained, and a hierarchical linear regression model was used to predict scores on Hood's Mysticism Scale, which had previously been used in research on the psychology of religion as well as the mystical experiences induced by the psychedelic drug psilocybin (Griffiths et al., 2006). As can be seen in Table 2, after

TABLE 2 **Hierarchical Linear Regression Model Predicting Hood's Mysticism Scale Scores in Substance Users from Demographic, Mood, and Typical Drug Dose Variables**

	Variable	*B*	β	*t*	R^2 Change
Step 1	Gender	−7.20	−0.09	−1.60	
	Age	0.24	0.08	1.35	
	Education	−2.07	−0.05	−0.87	0.02
Step 2	Gender	−6.69	−0.09	−1.48	
	Age	0.23	0.08	1.31	
	Education	−2.26	−0.06	−0.95	
	Depression	0.00	0.00	0.00	
	Anxiety	0.47	0.04	0.57	
	Stress	−1.16	−0.11	−1.42	0.01
Step 3	Gender	−7.25	−0.09	−1.57	
	Age	0.30	0.10	1.58	
	Education	−2.00	−0.05	−0.83	
	Depression	0.04	0.00	0.05	
	Anxiety	0.47	0.04	0.58	
	Stress	−1.18	−0.12	−1.42	
	Alcohol	−1.72	−0.04	−0.64	
	Cocaine	−0.48	−0.02	−0.22	
	Opiates	4.45	0.10	1.69	
	Cannabis	2.00	0.06	0.90	
	MDMA	2.21	0.06	0.98	0.02
Step 4	Gender	−10.44	−0.13	−2.31*	
	Age	0.42	0.14	2.26*	
	Education	−1.31	−0.03	−0.56	
	Depression	−0.04	−0.00	−0.05	
	Anxiety	0.19	0.02	0.24	
	Stress	−1.01	−0.10	−1.25	
	Alcohol	−1.40	−0.03	−0.53	
	Cocaine	−0.80	−0.02	−0.38	
	Opiates	3.51	0.08	1.38	
	Cannabis	0.25	0.01	0.12	
	MDMA	−1.65	−0.05	−0.70	
	Psilocybin	4.67	0.13	2.02*	
	LSD	8.49	0.23	3.60**	0.07**

B, unstandardized regression coefficients; β, standardized coefficients; *t*, *t*-test statistics; R^2 change, change coefficient; MDMA, methylenedioxymethamphetamine; LSD, lysergic acid diethylamide; *$p<0.05$; **$p<0.0001$.
From data collected by Lyvers and Meester (2012).

controlling for age, gender, education level, and mood scores on the Depression Anxiety Stress Scales, the use of LSD or psilocybin was significantly positively related to Mysticism Scale scores in a dose-related fashion, whereas the use of MDMA, cannabis, cocaine, opiates, or alcohol was unrelated to Mysticism Scale scores. Similarly, an earlier survey by Lerner and Lyvers (2006) found that, in comparison to users of nonpsychedelic drugs, users of psychedelic drugs (primarily LSD) scored significantly higher on a measure of mystical beliefs (the Mystical Beliefs Questionnaire) and on the Life Values Inventory values of spirituality, concern for others, concern for the environment, and creativity but lower on the value of financial prosperity (see Table 3). The findings indicated a more spiritual and less materialistic orientation among users of psychedelic drugs compared to users of nonpsychedelic drugs. Whether such differences in beliefs and values were a result of LSD-induced mystical experiences or perhaps reflected characteristics of those inclined to take LSD is unclear.

TABLE 3 Scores on Mystical Beliefs Questionnaire and Selected Life Values from the Life Values Inventory (LVI) for Psychedelic Drug Users Compared to Users of Nonpsychedelic Drugs

	Users of Psychedelics	Users of Other Drugs
Questionnaire Scores	**($n = 88$)**	**($n = 93$)**
Mystical beliefs***	64.13	33.29
LVI spirituality***	12.18	8.65
LVI concern for environment**	12.19	11.01
LVI concern for others**	12.25	11.51
LVI creativity*	11.94	10.88
LVI financial prosperity***	8.67	10.80

*$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$.
From data collected by Lerner and Lyvers (2006).

TWO SIDES OF LSD

Some very strong claims have been made about psychedelic drugs, particularly LSD. On the positive side, proponents claim that when used properly psychedelics can provide deep and lasting insights about the nature of reality and about oneself—insights that may promote desirable personal qualities such as creativity, open-mindedness, pacifism, and compassion in at least some users (Lerner & Lyvers, 2006; Lyvers & Meester, 2012; MacLean et al., 2011), as well as potentially facilitating recovery from alcoholism (Krebs & Johansen, 2012) and alleviation of end-of-life anxiety (Gasser et al., 2014). On the negative side, adverse outcomes of casual psychedelic drug use are well documented and include panic reactions and psychotic episodes followed by lasting depression, anxiety or (rarely) psychotic disorder (Cohen, 1970; Hofmann, 1983). So-called LSD flashbacks—brief, unpredictable, and uncontrollable posttrip recurrences of perceptual or other phenomena experienced on the drug—are usually temporary and may reflect PTSD-like sequelae of overly intense psychedelic experiences, especially bad trips. Flashbacks generally subside within a few months following the last psychedelic use. A much rarer and more problematic syndrome is hallucinogen persisting perceptual disorder (HPPD), which may last for years after psychedelic use and which seems to be particularly associated with LSD. In HPPD, visual patterns like those seen on a psychedelic trip are overlaid on normal visual perception, or visual perception is distorted in some way, often accompanied by disturbing feelings of dissociation or depersonalization (Halpern & Pope, 2003). Benzodiazepines have reportedly proven effective for many HPPD sufferers, suggesting that HPPD may be an unusual subtype of anxiety disorder associated with LSD use. In any case, adverse drug reactions and aftereffects appear to be rare when LSD or other psychedelics are administered in a clinical setting following proper safety guidelines (Johnson et al., 2008).

APPLICATIONS TO ADDICTIONS AND SUBSTANCE MISUSE

As discussed earlier, LSD and other classic psychedelics are not addictive and have zero reinforcement potential in animal models of drug use. They are thus quite unlike other abused substances that commonly elicit compulsive patterns of drug self-administration in humans and laboratory animals, such as alcohol, nicotine, cocaine, amphetamines, and opioids. LSD elicits anxiogenic responses and signs of hallucination in nonhuman mammals, including higher primates. Further, LSD has a very high therapeutic index with lethal overdose extremely unlikely; even accidental ingestion of many hundreds of times the typical psychedelic dose has not resulted in death. For these reasons LSD cannot be evaluated in the same way as alcohol, nicotine, cocaine, methamphetamine, or heroin—drugs associated with significant risk of physical toxicity and addiction. Indeed, as described above, LSD has been used with some success to treat chronic alcoholism. Nevertheless LSD and other psychedelics can certainly be abused in the sense that casual use entails a significant risk of harm to self or others. Highly disorganized behaviors under the acute influence of the drug, and adverse psychological sequelae such as panic attacks, flashbacks, psychotic reactions, and suicides, have been reported. The subjective effects of LSD are unpredictable, hence previous positive experiences are no guarantee against an adverse reaction. LSD is an extremely powerful mind-shaker that ideally should be taken only by mentally stable individuals under controlled, supervised conditions following established safety guidelines with adequate preparation (Johnson et al., 2008).

In conclusion, LSD and other psychedelics have shown promise in treating alcoholism and other disorders, as well as potentially providing insights into mind and brain, but even Timothy Leary eventually concluded that we must learn how to use them appropriately to minimize risks (Leary, 1982). Given the recent renaissance in human trials of potential clinical applications of LSD and psilocybin (Gasser et al., 2014; Moreno, Wiegand, Taitano, & Delgado, 2006), history suggests that a much more cautious approach to these fascinating mind-changing agents is definitely warranted this time around.

DEFINITION OF TERMS

Active placebo This is a placebo treatment that elicits a noticeable effect in subjects but which is not the effect of the experimental treatment under investigation.

Agonist This is a chemical that increases neurotransmission at receptors for a particular neurotransmitter.

Anxiogenic This refers to a substance causing or promoting anxiety.

Autognostic This is an adjective meaning of, or related to, or characterized by autognosis (self-knowledge).

Direct agonist This is a chemical that binds to and activates receptors for a particular neurotransmitter.

Double blind This refers to an experimental design in which neither the subjects nor the primary researchers know which treatment each subject is receiving, to avoid potential influence of bias on outcome.

Entactogen This is a type of drug with partial psychedelic properties such as MDMA (ecstasy) and related compounds and refers to the ability of such drugs to promote personal introspection ("touch within").

Entheogen This is an alternative term for full psychedelic drugs such as LSD and psilocybin, referring to the ability of such drugs to evoke transpersonal knowledge of "God within."

Mystical experience This refers to an acute awareness of a transcendent ultimate reality or God.

Psychedelic Literally "mind-manifesting," in its original usage this term refers to a unique class of hallucinogens such as LSD, psilocybin, and mescaline, which share serotonin agonist properties and a capacity to induce brilliantly colored visions, extreme alterations of consciousness, and mystical experiences. It also refers to a type of psychotherapy conducted in the 1950s and 1960s in which a large dose of LSD was administered on only one or two occasions with the goal of inducing a life-changing mystical experience.

Psycholytic Meaning "mind-loosening," this refers to a type of psychotherapy conducted in the 1950s and 1960s in which relatively low doses of LSD were administered during psychodynamic therapy to facilitate the emergence of repressed material.

KEY FACTS

- LSD is an extremely potent semisynthetic psychedelic drug with excitatory serotonin agonist actions in the brain.
- The threshold dose of LSD is about 25 μg, with 75–200 μg required to induce psychedelic effects.
- The profound mental changes triggered by LSD do not resemble endogenous psychotic states or dream states; however, the mystical experiences sometimes reported by LSD users share similar features with the mystical aspects of near-death experiences and the mystical experiences reported by followers of religious traditions aimed at achieving spiritual enlightenment, such as Zen Buddhism.
- LSD has previously shown promise in the treatment of severe chronic alcoholism, using a single high dose to elicit a transformative mystical/religious experience in the belief that such insight will promote long-term sobriety.
- LSD is a landmark drug in the history of efforts to understand mind and brain; however, attempts in the 1960s to portray LSD as the solution to all human problems led to widespread casual use, which exposed many to serious psychological hazards.
- Whether for medical, psychiatric, or spiritual purposes, LSD should be administered only following strict safety guidelines to minimize the risk of adverse psychological reactions.

SUMMARY POINTS

- This chapter presents an overview of LSD, an extremely potent semisynthetic psychedelic drug with serotonin agonist actions in the brain.
- The psychedelic properties of LSD were discovered by Swiss chemist Albert Hofmann in 1943.
- Initial interpretation was that the drug caused a "model psychosis" or temporary chemically induced schizophrenia, but eventually it was recognized that the experiences induced by LSD generally do not resemble endogenous psychoses.
- In the 1950s LSD was administered as a psychotherapeutic agent in the belief that it would unlock repressed memories and emotions. However, patients treated with LSD often reported transformative experiences of a mystical/religious nature, especially when higher doses were given.
- LSD was administered to thousands of alcoholics in the 1950s and 1960s in the belief that the ego-shattering effect of the drug would equate to "hitting rock bottom" and awaken a spiritual consciousness essential to achieving long-term sobriety.
- A meta-analytic study of earlier trials of the effectiveness of a single high dose of LSD to treat severe chronic alcoholism showed that this approach compared favorably to current pharmacotherapies.
- In the 1960s Harvard psychologist Timothy Leary promoted LSD as a quick route to spiritual enlightenment for the masses; he believed LSD had the power to transform society; however, such advocacy led to the illegalization of LSD, which came to be widely regarded as a threat instead of a panacea.
- Leary's promotion of LSD was regarded as reckless by those who had worked with the drug in a clinical or scientific context, and the result of Leary's (and others') proselytization was a near-total shutdown of research into the potential beneficial applications of LSD.
- Although physically a safe drug with a very high therapeutic index, the psychological effects of LSD can be extremely intense and have led to panic reactions and psychotic episodes, with sequelae including posttraumatic stress symptomatology.
- LSD shows promise for treatment of alcoholism and some other conditions; however, it should be administered only following strict safety guidelines to minimize the risk of adverse psychological reactions.

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