Chapter 80

Schizophrenia Modeling Using Lysergic Acid Diethylamide

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Abbreviations

DOI 2,5-dimethoxy-4-iodoamphetamine
LSD Lysergic acid diethylamide

THE HISTORY OF LYSERGIC ACID DIETHYLAMIDE, SEROTONIN, AND MENTAL DISEASE

Our current understanding of schizophrenia as a psychiatric disorder having a biological basis, rather than being just the product of a conflicted mind, is tied closely to the discoveries of both lysergic acid diethylamide (LSD) and the natural neurotransmitter serotonin. Although the Swiss chemist Albert Hofmann (1979) first synthesized LSD in 1938, it was not until 5 years later, in 1943, that he accidently ingested a minute quantity and discovered its unique psychoactive properties. The first scientific report proposing that the behavioral effects of intoxication by LSD resembled psychosis was published in 1947 (Stoll, 1947), the same year that LSD was made commercially available by the Swiss pharmaceutical company Sandoz. LSD was sold under the brand name Delysid and marketed as a tool for potential psychiatric treatment. Some sources have reported that Sandoz recommended that psychiatrists take the drug to "gain an understanding of the subjective experiences of the schizophrenic" (Ulrich & Patten, 1991). In 1950, the first report on LSD as an aid to psychotherapy appeared (Johnson & Busch, 1950). The authors gave LSD to 29 institutionalized psychiatric patients, most of whom had some form of schizophrenia. They noted that a few of the patients had profound experiences and were able to organize their ideas better, and two of them required no further treatment after their LSD experience (Johnson & Busch, 1950).

In 1937, only 1 year before LSD was first synthesized, Vittorio Erspamer identified a substance from enterochromaffin cells of the gut that caused smooth muscle contraction and named it enteramine (Erspamer & Vialli, 1937) (Figure 1). For several years Erspamer and his colleagues studied the effects of enteramine in various tissue systems, including mollusk heart and salivary gland of the octopus. In 1948, Maurice Rapport and Irvine Page at the Cleveland Clinic isolated a substance from coagulated cow blood that had vasoconstrictive properties and named it serotonin (Rapport, Green, & Page, 1948). The chemical structure of serotonin was elucidated in 1949 and determined to be 5-hydroxytryptamine (Rapport, 1949). It was not until several years later, in 1952, that enteramine and serotonin were shown to be one and the same molecule. It was established soon thereafter that serotonin was present in the brain (Twarog & Page, 1953). Gaddum reported in 1953 that the chemical structure of serotonin was embedded within the structure of LSD and remarked that because LSD affected the brain, where serotonin was also found, that LSD might interact with serotonin systems (Figure 2). Indeed, Gaddum found that LSD was able to block the contractile effects of serotonin on rat uterine tissue.

The pieces of the puzzle were put together in a paper by Woolley and Shaw (1954), where they "conceived the idea that the mental disturbances caused by lysergic acid diethylamide were to be attributed to an interference with the action of serotonin in the brain." They further noted that other drugs, including yohimbine and harmala alkaloids, which also cause some degree of "mental disturbances," have a structural resemblance to serotonin (Woolley & Shaw, 1954). Their thesis was that mental disorders like schizophrenia had a biological basis, a revolutionary idea for the time. About the same time, Gaddum (1955), who was performing experiments with LSD as an "antimetabolite" of serotonin, stated "it is possible that the 5-hydroxytryptamine in our brains plays an essential part in keeping us sane…."

The notion of LSD, and other classic hallucinogens, being used as tools to model schizophrenia and psychosis faded from prominence when the dopamine hypothesis of schizophrenia was formulated later, in the 1950s (Baumeister & Francis, 2002). Nonetheless, and despite heavy restrictions on its availability, LSD and other hallucinogens continued to be studied by a small number of scientists as tools to understand serotonin neuropharmacology. With the introduction of the atypical antipsychotic medications in 1989 (Meltzer, 1989), which have a higher affinity for blockade of certain serotonin receptors than dopamine receptors, there was a renewed appreciation for the role of serotonin in schizophrenia and psychosis and interest in using classic hallucinogens as tools to investigate the biology of these disorders. Today, there are several basic science and clinical research programs using the classic hallucinogens LSD and psilocybin to model certain aspects of schizophrenia and to understand essential brain function.

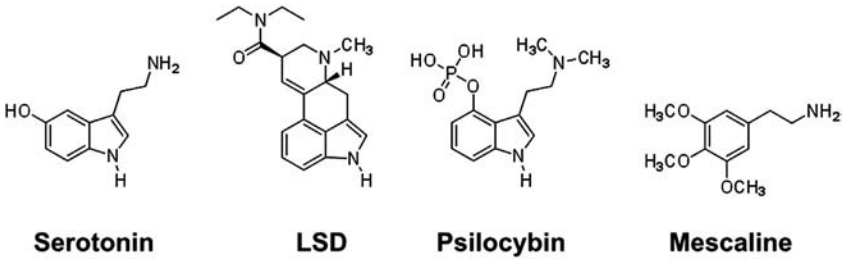

FIGURE 1 Structures of classic hallucinogens. The structure of serotonin is shown compared to that of other classic hallucinogens. Lysergic acid diethylamide (LSD) is a synthetic ergoline. Psilocybin is found naturally occurring in certain species of mushrooms. Mescaline is found naturally occurring in certain species of cactus like peyote. All have powerful hallucinogenic effects with similar acute subjective experiences resembling aspects of psychosis.

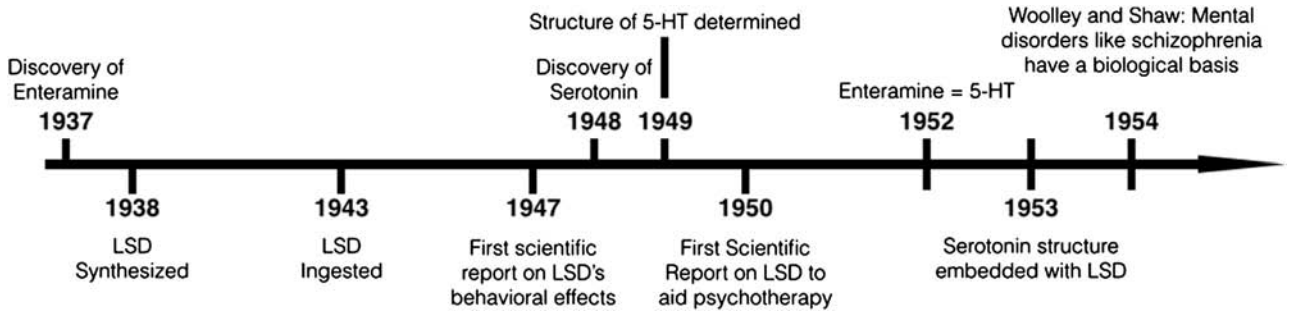

FIGURE 2 Timeline of the discovery of serotonin (5-HT) and lysergic acid diethylamide (LSD). The discoveries of serotonin, its structure, and LSD at about the same point in history are shown here. The observation that the structure of serotonin was embedded within the structure of LSD, and that LSD influenced the effects of serotonin, combined with the powerful behavioral effects of LSD led to the hypothesis that mental disorders like schizophrenia had a biological basis.

In humans, the classic hallucinogens all share in common activation of the serotonin 5-HT_{2A} receptor subtype to produce their intoxication. The acute effects can include visual distortions (e.g., geometric patterns, bright colors), auditory distortions (e.g., change in tonal or pitch perception), disorganized thought, time distortions, synesthesias, and detachment from reality (Nichols, 2004). Outright hallucinations usually occur only at higher doses, but they can manifest at lower doses in sensitive individuals. These acute effects are highly reminiscent of the symptoms of an acute psychotic break and the positive symptoms of schizophrenia (Vollenweider, 2007; Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998). Although most classic hallucinogens share these qualities, with minor subjective differences, LSD is unique. In humans, LSD can produce a biphasic behavioral response. The first phase is shared with the other drugs of this class and is characterized by visual distortions and hallucinations. There is a subsequent second phase, lasting an additional 4–6 h, that is darker, with ideas of reference and paranoid ideation (Freedman, 1984). The particular subset of paranoid-like alterations in mood that occurs within the second phase of the LSD experience closely resembles certain negative symptoms of schizophrenia. Work in rats has demonstrated a similar biphasic effect, in which animals can be trained to discriminate the subjective introspective cues of LSD between earlier and later time points. The early behaviors are entirely mediated by activation of the serotonin 5-HT_{2A} receptor, whereas the latter phase depends on activation of dopamine D2-like receptors (Marona-Lewicka & Nichols, 2007; Marona-Lewicka, Thisted, & Nichols, 2005).

Schizophrenia is now understood to be a complex mental disease with a diverse etiology, and there is a consensus that it is due to a defect in brain development caused by either genetics or an environmental insult in utero to the developing fetus (Fatemi & Folsom, 2009; Garey, 2010; Piper et al., 2012). Analysis of the brains of schizophrenia patients has indicated simultaneous dysfunction in the neurotransmitter systems for dopamine, serotonin, glutamate, and γ-aminobutyric acid (GABA), among others. The underlying mechanistic and developmental processes that lead to this dysfunction remain largely unknown and there have been no new FDA-approved drug-based therapeutic strategies to treat schizophrenia since the introduction of the atypical antipsychotic medications a quarter of a century ago. That has been due in part to a lack of good animal models. Models of schizophrenia or psychosis are challenging because schizophrenia is a disorder that is unique to humans. Early models employed blockade of the behavioral effects of dopaminergic agonists such as apomorphine or amphetamine. More recently accepted models employ the acute administration of drugs whose effects are thought to resemble psychosis, such as phencyclidine (PCP). These models are problematic because they rely on the presence or recent presence of the drug on board to produce their effects. Further, they do not represent what occurs in the *onset* of psychosis, which is usually not precipitated by drug use and is an idiopathic process likely to be mediated by gradual changes in cellular function. Nevertheless, these traditional models have provided key insights into certain aspects of schizophrenia. Although the dopamine agonist and *N*-methyl-D-aspartate

(NMDA) antagonist models have garnered the most attention and have generated the bulk of data with regard to what is known about the molecular and cellular aspects of schizophrenia, attention has returned to the classic hallucinogens for study.

HUMAN MODELS OF SCHIZOPHRENIA AND PSYCHOSIS USING LSD

The first models of psychosis using LSD were actually human experiments that took place in the 1950s. At that time, behavioral pharmacology in animal models was in its infancy, and humans were often the primary research organism. Institutional review board regulations were lax to nonexistent, allowing researchers to perform kinds of experiments in humans that today would be ill-advised or not even possible. Nevertheless, those experiments provided important clues and insight into LSD, serotonin, and mental disease. Although another natural product, mescaline, had previously been believed to produce behaviors similar to psychosis, the dose of LSD necessary to produce similar effects was orders of magnitude lower. This extreme potency was a key factor in the high interest and further examination of LSD and spurred theories that there was perhaps an endogenous molecule similar to LSD naturally occurring in the brain that if in excess could lead to psychosis. Indeed, early on the behavioral effects of LSD were often referred to as "LSD-psychosis" (Bercel, Travis, Olinger, & Dreikurs, 1956). An early study by Bercel examining the effects of LSD on normal subjects characterized many behavioral and physiological effects of LSD ranging from handwriting, finger tapping, memory, visual effects, electroencephalography, time distortion, and paranoia, among many others, and concluded that "(LSD) given to normal adults produced wide-spread temporary alterations in psychic functioning which resembles most the undeteriorated schizophrenic reaction type" (Bercel et al., 1956).

Throughout the 1950s there continued to be several reports on the behavioral and physiological effects of LSD and the effects of various drugs on these actions. Interestingly, in addition to using LSD to mimic psychosis, much research also was directed toward developing LSD as a tool to use in psychotherapy to treat not only schizophrenia, but other disorders such as addiction. It was recognized, however, that despite the numerous similarities between "LSD-psychosis" and schizophrenia there also were certain differences (Savage & Cholden, 1956). For example, although auditory hallucinations can occur after LSD administration, they occur with much higher frequency in schizophrenics. Further, whereas paranoia and delusions are common to both LSD and schizophrenia, delusions of persecution or being under the influence of another are four times less frequent with LSD than in schizophrenia (Savage & Cholden, 1956). To exploit the similarities between LSD and psychosis, the U.S. government initiated a program in the early 1950s that was code-named MKUltra, which lasted until 1973, to use LSD as well as other psychoactive drugs to produce mental disturbances as a possible means of "mind control" or interrogation.

Amid the social upheaval of the 1960s LSD was classified in the United States in 1968 as an illegal and dangerous drug with no medical value. As a consequence, just as ethical standards of research were also improving, human studies with LSD virtually ended. Literature reports on LSD shifted more toward aspects of drug abuse, epidemiology, case studies, and use in animal models. After achieving a high of 1786 research publications (found using the term "lysergic acid diethylamide" in the PubMed database) for the decade of the 1970s, there were only 293 for the entire decade of the 2000s, only 26 of which also included the search term "schizophrenia." In the late 1990s clinical experimentation with hallucinogens in humans resumed after a nearly 20-year absence, led largely by German psychiatrists Leo Hermle, Euphrosyne Gouzoulis-Mayfrank, and Manfred Spitzer and particularly by Swiss psychiatrist Franz Vollenweider. Rather than LSD, the centrally active component of psychedelic mushrooms, psilocybin, was used. In these studies, the drug was administered to healthy volunteers and the effects were measured using the rigor of modern scientific protocols and methods. The subjective effects on waking consciousness were measured using new psychological instruments, physiological effects were carefully measured, and, importantly, brain scans were performed to highlight areas within the brain responding to drug (e.g., see Vollenweider et al., 1997, 1998). Hyperactivity was seen in specific cortical areas including the frontal cortex and it was noted that "The common effect of these drugs appears to parallel comparable metabolic changes associated with acute psychotic episodes in schizophrenics and contrasts with the hypofrontality seen in chronic schizophrenic patients" (Vollenweider et al., 1997). The main conclusions were consistent with those of 40 years earlier comparing the acute effects of LSD to an acute psychotic break in a schizophrenic individual (see Table 1). In a follow-up report the next year, Vollenweider et al. (1998) demonstrated that the psychosis-like behavioral syndrome induced by psilocybin was indeed mediated by activation of the serotonin 5-HT_{2A} receptor. Previous data from animal models had indicated that the behavioral effects of the classic hallucinogens were induced by activation of this receptor, but it was proved also to be valid in humans only when the effects of psilocybin were completely blocked by a selective 5-HT_{2A} receptor antagonist in humans, demonstrating that 5-HT_{2A} receptor activation was both necessary and sufficient for the psychosis-like effects of psilocybin (Vollenweider et al., 1998).

Given the similarity of "LSD-psychosis" to schizophrenia, and the singular requirement for activation of the serotonin 5-HT_{2A} receptor for the behavioral effects of LSD, it would be anticipated that antagonism of the 5-HT_{2A} receptor would be therapeutic for schizophrenia. Indeed, a key feature of the atypical antipsychotic medications, which were reported to have greater efficacy against the negative symptoms than earlier antipsychotics, is that they have high-affinity blocking activity at the 5-HT_{2A} receptor. When, however, the selective 5-HT_{2A} receptor antagonist M100907 was tested for treatment of schizophrenia in the late 1990s, it failed in its phase III clinical trial (de Paulis, 2001) and has not been tested again as a therapeutic for schizophrenia. A newer selective 5-HT_{2A} receptor antagonist, Pimavanserin, has shown good efficacy in late-phase clinical trials for the treatment of psychosis associated with Parkinson disease (Cummings et al., 2014).

The effects of psilocybin on cortical network activity in the human brain have been examined by functional magnetic resonance imaging. In that study, an increase in functional connectivity was observed between the default mode and the task-positive network after administration of psilocybin, with a preserved thalamocortical functional connectivity (Carhart-Harris et al.,

TABLE 1 Similarity of hallucinogenic behavior to schizophrenia

	Psilocybin	Schizophrenia
Psychopathology		
Positive Symptoms		
• Hallucinations/illusions	++	++
• Delusions	+	++
• Thought disorder	+	++
Negative Symptoms		
• Blunted affect	0 to +	++
• Withdrawal	+	++
Depersonalization	+ to ++	++
Derealization	+	++
Neuropsychology		
• Attention disturbance	+ to ++	++
• Distractibility	+	++
• Working memory	+	++
• Associative deficits	+	++
• Planning/mental flexibility	++	++
Cortical Activity		
• Frontal (PET)	++	++

A comparison of the acute behavioral effects of a classic hallucinogen, psilocybin, with effects similar to those of LSD is shown. There is considerable conservation of key behavioral and physiological effects. PET, positron emission tomography.
Adapted from: Vollenweider (2001).

2013). Similar network activity is observed in early psychosis, and the authors proposed that the conserved changes in network activity underlie aspects of the similarity between the psychedelic state and early psychosis (Carhart-Harris et al., 2013). The same group has also reported on the results of the first clinical use of LSD since the early 1980s that examined the mental effects of LSD in healthy volunteers (Carhart-Harris et al., 2014), although no comparisons to schizophrenia were drawn in that study.

EARLY ANIMAL MODELS

Surprisingly, one of the earliest animal models used to study LSD was the Siamese fighting fish, *Betta splendens*. In the first of many such reports using *B. splendens*, it was suggested that the sensitive response of the fish to LSD could be used not only as a bioassay for the detection of LSD in urine, but also to test for psychosis-producing substances in the urine of schizophrenics (Abramson & Evans, 1954). A subsequent paper reported on just such an experiment, in which the authors placed the fish in the urine of schizophrenics and measured the effects on swimming behavior. The conclusion of the report was that this particular assay was not useful in identifying schizophrenia-related metabolites in patients' urine (Moody & Smith, 1956).

The first attempt at modeling psychosis in the mouse was reported by Woolley in 1955, who observed that mice administered LSD predominantly walked backward in a prone position, as if backing up on an inclined plane. In that paper Woolley (1955) remarked: "Is the abnormal behavior of the LSD-25 mice the result of a psychosis? One can never tell with certainty what a mouse is thinking of, and consequently it is not possible to answer this question objectively. However, because of the resemblance of the behavior of an LSD-25 mouse to that of a normal mouse on an inclined plane, the use of the working hypothesis seems to have some basis for justification." The first report of the effects of LSD in a rat appeared a year later, and in addition to overall observations, the ability of a rat trained to climb a rope was examined under the influence of LSD (Winter & Flataker, 1956). Although both mice and rats were used for numerous studies in the 1950s through the 1970s to examine various effects of LSD, they were primarily utilized as models to understand serotonin neuropharmacology better. It was not until 1980 that rats administered LSD were once again proposed to serve as a model for schizophrenia. Braff and Geyer (1980) examined the effect of LSD on the startle response in rats and noted a similarity with that occurring in schizophrenics. The startle response, or prepulse inhibition (PPI), is an assay that measures sensory-motor gating, or the ability of an initial acoustic event to attenuate the magnitude of the startle

response to a stronger subsequent acoustic event. At a fundamental level, PPI is believed to be a measure of cognition and the ability of an individual to filter out unnecessary sensory information (Braff & Geyer, 1980).

Behavioral pharmacological studies in the 1990s with LSD and related hallucinogens examined outcomes like PPI and electrophysiological studies of rat brains in slice culture to examine the circuitry underlying the hallucinogen response. These experiments led to a greater understanding of how serotonin is involved in normal cognitive function and how dysfunction of serotonin systems may be involved in schizophrenia. Importantly, this work led to the understanding that the behaviors LSD produces are not just a function of modulation of the serotonin system, but that additional neurotransmitters such as dopamine and glutamate are also significantly influenced by LSD. Importantly, how LSD influences serotonin, dopamine, and glutamate at the cellular level is highly conserved with other rodent models of schizophrenia like the NMDA antagonist/PCP model, as well as with the dysfunction of these major neurotransmitter systems found in schizophrenia brains (Aghajanian & Marek, 2000; Marek & Aghajanian, 1998).

CURRENT RODENT MODELS OF SCHIZOPHRENIA OR PSYCHOSIS USING LSD

In the present era, several different groups have again proposed using classic hallucinogens, including LSD, to model schizophrenia and psychosis (Halberstadt & Geyer, n.d.; Hanks & González-Maeso, 2013; Marona-Lewicka, Nichols, & Nichols, 2011). More precisely, LSD has been used to model and study in rodents specific aspects of behaviors and pathology that have been observed in human schizophrenics. These include disruptions in PPI, exploratory behavior, and social interactions, among others. Although both mice and rats are currently used, the neuropharmacology of hallucinogens in humans is more similar to that in rats than in mice. In the mouse, tryptamine-based hallucinogens are metabolized by monoamine oxidase A within only a few minutes of administration. For example, the half-life of LSD in the mouse is less than 10 min, and the effects of acute LSD on sensitive behaviors such as drug discrimination are apparent for only a short window of time (Benneyworth, Smith, Barrett, & Sanders-Bush, 2005). In the rat, as well as in humans, the behavioral effects of LSD can be detected for several hours after an acute administration. Another significant difference is that in mice, a significant component of LSD's interoceptive cue (~50%) is mediated by activation of the 5-HT_{1A} receptor (Benneyworth et al., 2005). This finding contrasts with what has been observed in rats and humans, in which there is very little, if any, significant component of 5-HT_{1A} receptor activation in the interoceptive cues produced (Reissig, Eckler, Rabin, & Winter, 2005; Vollenweider et al., 1998). Although we do not know if a rodent hallucinates, the subjective feeling of what an animal experiences after drug administration, as measured by drug discrimination, can tell us much about the subjective effects in humans. An assay in the mouse in which the effects of LSD can be measured is the head-twitch response (Canal & Morgan, 2012). Unfortunately, it is not a measure of the subjective effect of the drug, and several drugs that are not hallucinogenic also can produce this response. Further, whereas there is a substantial 5-HT_{1A} receptor-mediated component to the LSD interoceptive cue in the mouse, there is no contribution from activation of this receptor to the head-twitch response. Therefore, the head-twitch response in mice should not be considered a reliable proxy for "hallucinogenic behaviors" in humans.

For the phenethylamine-based hallucinogens, like 2,5-dimethoxy-4-iodoamphetamine (DOI), the pharmacology is more similar between mouse, rat, and human. The majority of measurable behaviors elicited are due to 5-HT_{2A} receptor activation and can be detected for several hours after an acute administration in the mouse (Smith, Barrett, & Sanders-Bush, 2003). The mouse has been highly informative on the neuropharmacology of serotonin 5-HT_{2A} receptor function using fairly selective phenethylamine 5-HT_2 receptor agonists such as DOI, as well as genetic knockouts for the receptor. This model is less relevant, however, to study schizophrenia as a disease. As mentioned above, LSD is unique among hallucinogens with its pronounced biphasic effects in humans, which also are evident in rats, and includes behaviors relevant to the positive as well as the negative symptoms of schizophrenia.

Using LSD in a rat to model schizophrenia or psychosis, two different approaches have been taken. The first involves the study of the acute effects of LSD on the brain and behavior. These have been the typical studies employed by numerous groups investigating cognitive function, social interaction, locomotor effect, etc. Additionally, several informative studies have been carried out in rat brain slices examining cortical network activity (Aghajanian, 2009). The bulk of these studies have, however, been performed in rats during the first phase of induced behaviors. How these individual behaviors change over the time course of the drug, with few exceptions, has not been explored (Marona-Lewicka et al., 2005), but such studies may be informative on certain aspects of schizophrenia. A more recently proposed model involves chronic treatment with LSD. In this model, LSD is administered every other day for 3 months. During the course of treatment, abnormal behaviors appear that include increased locomotion, anhedonia, and social deficits that are similar to behaviors observed in other rodent models of schizophrenia (Marona-Lewicka et al., 2011). In this case the model involves study of the animal several weeks after LSD administration has ceased because the drug-induced abnormal behaviors persist for at least many months without the drug on board. Molecular analysis of the brains from these animals 1 month after drug discontinuation shows a dysfunction in dopamine, glutamate, and GABA systems and a significant enrichment of misexpressed genes implicated in schizophrenia (Martin, Marona-Lewicka, Nichols, & Nichols, 2014). Unlike the examination of the acute effects of LSD in the rat, this model may more accurately model the negative aspects of schizophrenia. Other animal models that have been used to study the effects of hallucinogens include primates and invertebrates (Li, Rice, & France, 2008; Nichols, Ronesi, Pratt, & Sanders-Bush, 2002). These models, however, are not widely used.

SUMMARY

LSD has a long and intertwined history with neuropsychiatric diseases like schizophrenia and psychosis. It played an important role

in the first understanding that psychosis has a biological basis and in helping to inform the molecular genetic basis of the etiology of schizophrenia through its use in animal models. Although schizophrenia is a uniquely human disease, animal models employing LSD, and other drugs like PCP, as well as genetic models, together have been very informative as to the etiology of schizophrenia and psychosis and will continue to be extremely valuable in the study of these diseases.

SUMMARY POINTS

- The near-simultaneous discovery of LSD and serotonin led to the notion that psychosis has a biological basis that involves serotonin.
- Early studies attempted to model psychosis and schizophrenia in humans with LSD.
- Subsequent to the use of LSD models in humans, animal models were developed.
- Studies using LSD to study schizophrenia and psychosis were halted for several years.
- There is a renewed interest in using LSD to model and study schizophrenia in animal models.
- Contemporary animal models have been highly informative with respect to serotonin neuropharmacology and schizophrenia.

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