Hallucinogens and Schizophrenia

Use of the term ‘hallucinogen’ immediately calls into question the precise meaning of the word. Literally, it means ‘a substance that induces hallucinations’, where ‘hallucination’ is defined as ‘a false perception occurring without any true sensory stimulus’. However, whether drugs described as hallucinogens actually produce true hallucinations is disputable. The term was introduced by Hoffer and Osmond in 1957 to describe ‘a substance that in small doses can alter perception, thought and mood to create illusions in the mind of the user’. Perhaps a more accurate term is ‘phantasticants’ (Shulgin, 1978) or ‘illusogens’ (Brown and Branden, 1987) to imply a distortion of perceived reality, as opposed to producing true hallucinations superimposed on the environment. A more popular term is ‘psychedelic’, coined by Osmond in 1957, meaning ‘mind-manifesting’. This term is also more widely used in describing the culture and art forms related to the use of such drugs. However, for those reasons it lacks scientific credibility, so tends not to be used in the scientific community. Furthermore, the psychotropic aspects of these drugs are not confined to the altering of perception and the possibility that they may mimic or induce psychosis has been long been recognised. Hence the term ‘psychotomimetic’ is often synonymous with the above terminology. This so-called psychotomimetic activity of hallucinogens is the focus of this essay, whereby the psychological effects of these drugs are compared to the symptomatology of schizophrenia, in an attempt to evaluate the possible physiological defects proposed in the pathology of schizophrenia. Of course, the extent of the similarity between the drug-induced ‘psychosis’ and the psychotic symptoms of schizophrenia is a major determinant for the usefulness of hallucinogens for this purpose; a point to be further elaborated. While some social and historical aspects of the drugs are to be mentioned, this essay is not intended to encompass issues such as drug abuse and drug problems in society.

Much of the experimental study into hallucinogens was carried out in the 1960s-70s, and many of the books available for research date from around this age. This essay is therefore intended to provide, to some extent, a more historical account and not just a completely contemporary compilation of research.

As already noted, ‘hallucinogens’ is a fairly non-specific term to categorise quite a broad group of drugs, based entirely on their psychological effects. Classification of hallucinogens is often based upon their molecular structure (see table 1). The drugs discussed in this essay are of the phenylalkylamine and indolealkylamine (including LSD) structure groups, sometimes grouped together as the LSD-mescaline-psilocybin group. Members of the other categories will not be discussed any further.

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Mescaline (3,4,5-trimethoxyphenethylamine) (Fig. 1.a) is derived from the peyote cactus (*Lophophora williamsii*), from southwestern United States and Mexico. It is the prototypical phenylethylamine, of which many structural derivatives exist. The structure of mescaline is similar to noradrenaline (Fig. 1.b). Modification of the structure by substitution can increase or decrease its potency as a hallucinogen. The potency of mescaline is often used as a scale for the relative potency of other hallucinogens, expressed in mescaline units (MU) and calculated as the effective dose of mescaline divided by the effective dose of the drug in question. Perhaps one of the most famous and complete accounts of the effects of mescaline is “The Doors of Perception”, by Aldous Huxley, 1963.

Fig. 1.

![Mescaline](image1.png) ![Noradrenaline](image2.png)

a) Mescaline (3,4,5-trimethoxyphenethylamine)  

b) Noradrenaline

Psilocybin (N,N-dimethyl-4-phosphororyltryptamine) (Fig. 2.a) is the prototypical indolealkylamine. It is found in many species of mushrooms of the genera *Psilocybe*, *Panaeolus*, *Copelandia* and *Conocybe*. Psilocybin is dephosphorylated to psilocin (N,N-dimethyl-4-hydroxytryptamine) (Fig. 2.b) after ingestion, which is also found in the same mushrooms and is the active form. Its structure is similar to serotonin (Fig. 2.c), as it also contains the indole nucleus (Fig. 2.d).

Fig. 2.

![Psilocybin](image3.png) ![Psilocin](image4.png)

a) Psilocybin (N,N-dimethyl-4-phosphororyltryptamine)  

b) Psilocin (N,N-dimethyl-4-hydroxytryptamine)

c) Serotonin (5-hydroxytryptamine)  

d) Indole nucleus

Similar indoleamine compounds exist with hallucinogenic activity. One of which is DMT (N,N-dimethyltryptamine) (Fig. 3.a), found naturally in the plant *Mimosa hostilis* and is a component of various types of South American snuffs. It is inactive when taken orally, so must be sniffed,
smoked or injected to be effective. Another similar compound is bufotenine (N,N-dimethyl-5-hydroxytryptamine) (Fig. 3.b), derived from the mushroom *Amanita muscaria* and the skin of some toads (hence *bufo-* , a genus of toads). It is also found in a certain fish, *Kyphosus fuscus*. Its structure is very similar to serotonin, and is formed as a product of an unusual metabolic pathway of serotonin, proposed as a mechanism in some psychiatric disorders, discussed later in greater detail.

Fig. 3.

![DMT (N,N-dimethyltryptamine)](image)

![Bufotenine (N,N-dimethyl-5-hydroxytryptamine)](image)

LSD (lysergic acid diethylamide) (Fig. 4) is perhaps the most famous hallucinogen, since there is a greater volume of literature on LSD than any other psychotomimetic drug. It was first discovered to be psychoactive by Albert Hofmann in 1943, after he accidentally ingested some of the substance while researching ergot alkaloids. Lysergic acid occurs naturally in the ergot fungus. Use of LSD for medical research subsequently flourished, especially in the field of mental health, where its alleged ability to produce a model psychosis was studied. At the time, biochemistry of mental disorders was rudimentary and LSD appeared to offer some new light in this field. Its reputation in the lay community as a hallucinogen prompted a huge following, with the advent of the psychedelic era of the late 1960s to 1970s. It was outlawed in the US in 1965, and its use in research was drastically limited but illicit manufacture and abuse continued. It remains the most widely available hallucinogenic drug of abuse.

Fig. 4.

![LSD (lysergic acid diethylamide)](image)

The indolealkylamine hallucinogens bear a structural resemblance to serotonin (5-HT), suggesting that their mechanisms of action may be via effects on serotonergic systems. When these effects were first explored (by Freedman, 1961) LSD was discovered to increase 5-HT levels in the rat brain. Further investigation, using microiontophoretic techniques showed that LSD exerted an inhibitory effect on the firing of the serotonergic dorsal raphe neurones, more recently found to be via agonist actions at (presynaptic) 5-HT$_{1A}$ autoreceptors. Indeed the degree of inhibition of the raphe activity has been related to the relative hallucinogenic potencies of psilocybin, DMT and bufotenine. Since the dorsal raphe (DR) exerts an inhibitory effects on postsynaptic target cells (e.g. in the geniculate nucleus, optic tectum and limbic structures), LSD
produces excitation of these targets. The dorsal raphe is believed to filter sensations, therefore its decreased activity could produce an overload of sensory information. However, tolerance to LSD develops rapidly, within 4 days (producing decreased effects for a given dose) in spite of maintained inhibition of the raphe. The role of the dorsal raphe in hallucinogenesis is therefore thought to be less important than direct effects on the postsynaptic target neurones themselves. Postsynaptic 5-HT2 receptors have been identified as the main site of action. Indeed, tolerance to LSD in the rat is related to downregulation of 5-HT2 receptors.

Further development in selective 5-HT antagonists and identification of 5-HT receptor subtypes lead to the discovery that indolealkylamine and phenylalkylamine hallucinogens mediate their effects via the 5-HT2A receptor. Indeed cross-tolerance between LSD, psilocybin, mescaline and DMT suggests that they share a common mode of action. The role of the 5-HT2C receptor is considered less important since its desensitisation is unrelated to the hallucinogenic activity of DMT. LSD also appears to act as a partial agonist at dopamine D2 receptors, which suggests a more complex action in both serotonergic and dopaminergic systems. The effects of phenylethylamine and indoleamine hallucinogens as partial agonists at 5-HT2A receptors have been related to modulation of NMDA glutamate receptor-mediated psychological processes. Mescaline, having a structure more like noradrenaline than do the indoleamines, appears to have effects more related to noradrenergic transmission, however it cannot be classified as an agonist or antagonist.

The effects of the hallucinogens mentioned above are essentially similar and the main difference is the relative potencies of the drugs. LSD is the most potent hallucinogen known, having activity at doses of 10-15 µg, although doses of around 100 µg are sufficient for significant hallucinatory effects. Psilocin is approximately 1/200 as potent as LSD, while mescaline is about 1/3500 of the potency.

Hallucinogens produce both physical and psychological effects; the latter being their intended purpose. Unfortunately, during the more intense period of studies in humans, pharmacological analysis techniques were not sufficiently advanced to provide clearly reliable results and, before more recent technical advances followed, human experimentation with LSD was severely limited. Even so, many reports of the psychological effects do exist, however the subjective nature of the findings further compounds the paucity of useful data. Although not very constructive to mention, it may be worth noting that verbal description is a hopelessly inadequate means of conveying the nature of the subjective effects of these drugs. One might appreciate this shortcoming as like ‘describing colour to a blind man.’

The effects of LSD and similar hallucinogens have been expressed as three phases:

1. **Somatic effects:** sympathomimetic; dizziness; tremors; pupillary dilatation; blurred vision.
2. **Sensory/Perceptual effects:** sensory distortions; altered colour; illusions, pseudohallucinations, and true hallucinations (especially in darkened room); sharpened acoustic sensation; rarely, synaesthesias (perception of one sense modality as another).
3. **Psychic effects:** mood changes, alternating euphoria and depression; altered sense of time, either accelerated or slowed; tension leading to panic with frightening hallucinations, feelings of insanity; depersonalisation and derealisation.
The above phases are by no means discrete, with a great deal of overlap.\(^5\) Altered perception of body image is also common, with limbs seeming detached or absent and body size perceived as smaller or larger than normal.\(^19\) The second phase has often been described as the “TV show in the head”\(^5\) and its duration correlates with the plasma half-life of LSD.\(^6\) Visual phenomena are even present in blind people, provided they previously had vision.\(^19\) Visual imagery is often reported as several particular forms, involving moving geometric and coloured patterns.\(^8\) The effects follow the above sequence,\(^5,6\) over a duration of 8-12 hours,\(^7,19\) peaking after 2-4 hours.\(^2\) The effects of psilocybin, though psychologically similar, peak after about 1 hour and last only 1-2 hours thereafter.\(^11\) DMT is reported to have similar effects to LSD, but for a much shorter duration (45 min-1 hour, 1mg/kg i.m.).\(^7\) In particular, “a rapidly moving, multi-dimensional, kaleidoscopic display of intensely coloured abstract and multirepresentational images” has been reported with DMT.\(^20\) However, the reputed psychological effects of hallucinogens are variable between individuals, being based on subjective reports,\(^9\) dependent on the setting in which they were taken and for what purpose.\(^3,8\) Mescaline has many reports that it produces a more sensual experience\(^7\) with less anxiety and introspection than LSD.\(^3\) Furthermore, it has been suggested that not all humans are capable of achieving the psychotomimetic state induced by LSD.\(^21\)

Various longer lasting effects of LSD have been reported, even after the plasma level is undetectable.\(^2\) The “psychedelic afterglow”, which can last for weeks, comprises decreased anxiety and emotional changes “toward loving and harmonious affections”.\(^7\) Whether this is biochemical or psychological in origin remains unclear. On the other hand, acute panic reactions are quite common, known as “bad trips”, but only last for a few hours.\(^5\) Perceptual changes may occur for a day or two following a particularly bad reaction or, rarely, recollection of frightening feelings during a “bad trip” may precipitate psychotic symptoms.\(^3\) Needless to say, such experiences are truly terrifying. Prolonged psychosis is a possible (but uncommon) outcome\(^5\) and bears a very close resemblance to acute schizophrenia.\(^22\) Such a reaction may only be precipitated in vulnerable people\(^5,6\) and is probably not a remaining effect of the drug.\(^3\) Flashbacks (acute, unpredictable recurrences of phenomena experienced under LSD) are often reported, sometimes years after the drug was last taken. Their cause remains unsolved.\(^5\)

The relationship between hallucinogens and mental illness has long been recognised, though interpreted in various ways according to different cultural and religious circumstances. For example, in religious rituals of the Native Indians in Mexico, the peyote-induced state was believed to be contact to the spiritual world\(^5\) and inappropriate use of the peyote was believed to cause madness.\(^8\) Following the discovery of LSD and its profound effects on the mind, much research has been directed towards the possible role of hallucinogens as producing a ‘model psychosis’:\(^3,5,7\)

In order to assess the validity of hallucinogen-induced psychic effects as a model of schizophrenia the similarities and contrasts between the two states must be evaluated, in their clinical, experimental and physiological manifestations.

Much of the investigation into the neurophysiological aspects of hallucinogenesis is necessarily based on animal studies. The purpose of animal models of schizophrenia is to simulate specific aspects of the schizophrenic syndrome.\(^23\) The problem lies where correlation of physiological
parameters, in relation to animal behaviour, to psychological processes in humans is largely based on inference. This is such that experimental and clinical data are unfortunately ever distant.24

A thorough account of the clinical and diagnostic features of schizophrenia, although welcome for completeness, is beyond the scope of this essay. The list would be complicated by the heterogeneity of the condition;24 the several different theories about categorisation of the many pathological criteria;23 and explanation of the symptoms.3 Indeed such an account would be an essay in its own right. Only the fundamental aspects of the condition are mentioned here, because of their later relevance to drug-induced states.

Bleuler, who first coined the term ‘schizophrenia’ distinguished fundamental symptoms, caused by “disturbed psychic functions and affectivity”, from accessory symptoms, comprising hallucinations and delusions.5 Other distinctions have been made, into positive symptoms of hallucinations, delusions and thought disorder, and negative symptoms of flattened affect, social withdrawal and poverty of speech. Accordingly, the syndrome has been defined as Type I, characterised by mainly positive symptoms, acute onset and good response to neuroleptics, and Type II, characterised by mainly negative symptoms, chronic course and poor response to neuroleptics.23

Schizophrenic patients have been reported to be more resistant to the psychological and hallucinogenic effects than control subjects.19 Hallucinogens can exacerbate pre-existing psychiatric illness,4 producing verbal exteriorisation and increased psychomotor activity in schizophrenics. However, patients can distinguish between the drug-induced effects and their illness.3,19 Depersonalisation produced by LSD, especially in relation to body image and disintegration of the personality appears to mimic schizophrenia, however the consensus of opinion is that there are more differences than similarities.19 This “dissolving of ego-boundaries”, if frightening to the individual can produce a “bad trip”, just as fragmentation of the ego causes panic in schizophrenics.3 Another contrasting clinical finding is that LSD typically makes subjects highly suggestible, while schizophrenics are particularly resistant to suggestion.7

A questionnaire, directed at subacute and chronic schizophrenics and a group of normal subjects on LSD, was designed to compare specific components of the two syndromes. Most similarity was found in paranoid schizophrenics, with regard to feelings of unreality, lack of control, changes in meaning and suspiciousness, but differed in affective changes and altered body image.7 Essentially, the schizophrenic syndrome primarily involved disturbed thinking, while the drug-induced state mainly concerned altered perception.5 Also, experimental data on the clinical manifestation of the psilocybin-induced mental state, measured on the Altered State of Consciousness (APZ-OAV) scale, reveals findings very similar to those seen in incipient, as opposed to chronic, schizophrenia.11

A famous report, “The Doors of Perception”, by Aldous Huxley is an eloquent account of his experience with mescaline and it provides some useful insight into the subjective effects of hallucinogens. Huxley noticed himself that his drug-induced state was reminiscent of schizophrenia.3 However, one might ask, how could he have known, having never been schizophrenic?
Obversely, the subjective accounts by several acutely schizophrenic patients show similarities to psychedelic drug experiences. Just as the effects of hallucinogenic drugs can be pleasurable, so can the early stages of schizophrenia. Indeed, the adverse is also true where the “bad trip”, mentioned earlier, is associated with the same panic reactions as seen in schizophrenic breakdowns. Sensory sharpening, and thence perceptual flooding, as produced by hallucinogens, has been also expressed by some patients. Likewise, the ‘primary delusions’ of early schizophrenics, where insignificant occurrences take on huge (but unidentifiable) meaning and significance, are commonly part of drug-induced psychedelic experiences.

Some accounts also exist stating that schizophrenics are more likely to make associations between indirectly related words. Also, the presence of schizophrenia has been found to be somewhat associated with creative talent. Parallel to this lie anecdotal reports that hallucinogens are able to ‘enhance creativity’, upholding their label as psychedelic, or ‘mind expanding’. The truth of such claims is highly controversial, for creativity is itself a subjective concept. Timothy Leary is a famous advocate of hallucinogens’ creativity-enriching properties. One investigation into this relationship showed that psilocybin increased subjects’ association of indirectly related words, which could be subjectively experienced as increased creativity. The relatively few other attempts at objectively measuring creativity have been contradictory.

A well-documented experimental feature common to both hallucinogens and schizophrenia is deficits in sensory gating, indicated by deficient prepulse inhibition and habituation of the startle response. This feature offers a good opportunity for animal experimentation to relate to human symptoms, since the startle response is ubiquitous across species. Effects on habituation have been demonstrated to be mediated by agonist action at 5-HT2 receptors, associated with over-activity of dopaminergic pathways in the forebrain. Indeed the modulation of the startle response appears to involve complex interactions between several monoamines, with which the deficits in schizophrenia will need to be clarified.

Experimental observations of brain function in schizophrenics have revealed differences from normal patients. Both regional blood flow and metabolic imaging studies have shown a relative ‘hypofrontality’ compared to normal. More recently, using SPECT (single photon emission computed tomography), mescaline has been found to produce a more ‘hyperfrontal’ pattern. Similarly, regional metabolism under the effects of psilocybin also shows a hyperfrontal pattern which, although is unlike that seen in chronic schizophrenics, is similar to those of chronic schizophrenics in acute psychotic episodes.

A prominent theory that produced much of the research into the possibility of hallucinogens revealing insights into the pathology of schizophrenia was the “Transmethylation Hypothesis”. It followed the recognition that mescaline and DMT have similar structures to neurotransmitters, and proposed that ‘endogenous psychotogens’, methylated amines with hallucinogenic properties produced by some inborn error of metabolism, were involved in the pathophysiology of schizophrenia. Evidence for such a theory is equivocal. Increased urinary excretion of DMT has been correlated to the presence of psychotic symptoms, especially in schizophrenia. Indeed an enzyme responsible for the production of 2-phenylethylamine, AADC (aromatic L-amino acid decarboxylase), has been found to increase in activity following administration of LSD.
Bufotenine, as mentioned earlier, can be produced by an alternative pathway in the metabolism of serotonin. Plasma levels of bufotenine have been correlated to mental abnormalities, including schizophrenia, but these results have been contradicted. An early problem noted with this hypothesis is that although tolerance develops to hallucinogens, tolerance does not develop to the putative endogenous substance. Later, the lack of tolerance to DMT strengthened belief that it may have a role as an ‘endogenous psychotogen’. However, evidence against the theory has been produced, and the observation that hallucinogen-induced psychoses only represent some aspects of schizophrenia questions the very foundation of the hypothesis.

The dopamine hypothesis of schizophrenia suggests an overactivity of particular dopaminergic pathways, is subject to its own arguments for and against and is only to be mentioned here briefly. Its theory is the basis for the action of typical antipsychotics, and outside the scope of this essay. The possibility of a role for serotonin in schizophrenia emerged from the action of hallucinogens at 5-HT receptors and their reputed ability to model psychosis. Later, the efficacy of the atypical antipsychotics in relation to their 5-HT2 antagonist properties provided additional evidence in favour of this role. Furthermore, the interactions between serotonergic and dopaminergic systems have been described whereby increases of dopamine in the prefrontal cortex have been mediated by actions of serotonin, particularly at 5-HT1B receptors. Unfortunately, results of studies into alterations in 5-HT levels and 5-HT receptor binding in schizophrenics are inconsistent and contradictory. Evidence is mounting in support of the suggested role of multiple interactive neurotransmitters, particularly dopamine, serotonin and glutamate.

So it seems from various comparisons that the closest similarities lie between hallucinogen-induced effects and the acute, early phases of schizophrenia, while the greatest contrasts are in chronic schizophrenics. This stands to reason that, if hallucinogens do indeed offer a physiological model of psychosis, the rapid onset and relatively short duration of the effects could only mimic the acute symptoms of schizophrenia. Logically it stands therefore that if the chronic state (i.e. type II) is a syndrome secondary to the acute syndrome (i.e. type I), it cannot be mimicked by the sudden actions of a drug. Whether this action is in fact a model of schizophrenia at all calls on Bleuler’s argument, that

“The type of disease designated by us as schizophrenia can never by any means whatever be characterised by the presence of any particular isolated symptoms and not even by the apposition of any particular symptoms.”

Indeed the effects of the drugs do only mimic certain aspects of mental illness, that is, ‘particular isolated symptoms’. Bleuler therefore explains that psychotomimetic drugs have contributed to the understanding of the organic psychoses, not of schizophrenia.

Whether Bleuler’s view stands up in the face of modern advances in neuropsychopharmacology is a matter of opinion. What does remain, however, is that schizophrenia is still a fascinating mystery, one which may only be solved once the complexities of the relationship between the brain’s physical functioning and the depths of the human mind are unravelled.

References


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