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Adverse Reactions to Psychedelic Drugs

A Review of the Literature

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The use of naturally occurring and synthetically derived compounds for their "psychedelic" effects has been a part of human culture for thousands of years. The basic pharmacology of the major synthetic psychedelic compounds (primarily lysergic acid diethylamide [LSD]-25) is described and reference is made to their potentially beneficial psychological effects.

Adverse reactions, defined as dysphoric and/or maladaptive/dysfunctional responses to the use of these drugs, sometimes require careful clinical judgment in order to diagnose. These reactions can be effectively classified along a temporal continuum. Acute, short-lived reactions are often fairly benign, whereas chronic, unremitting courses carry a poor prognosis. Delayed, intermittent phenomena ("flashbacks") and LSD-precipitated functional disorders that usually respond to treatment appropriate for the non-psychedelic-precipitated illnesses they resemble, round out this temporal means of classification. The question of organic brain damage as well as permanent changes in personality, attitudes, and creativity in patients and normals who have repeatedly ingested psychedelic drugs is controversial, but tends to point to subtle or nonsignificant changes.

Future areas for study of the psychedelics' pharmacological, psychological, and therapeutic effects are suggested.

History

The use of naturally occurring, exogenously administered substances for inducing altered states of consciousness extends back to ancient times. Cannabis products and certain species of mushrooms were used as long ago as the time of the Vedas, in India, nearly 5000 B.C. In the New World, mushrooms and certain cacti, barks, and vines were employed for similar purposes by indigenous cultures (147). Abuse apparently was fairly rare, perhaps because careful cultural, religious, and social proscriptions determined a uniform manner in which these substances were used and the experiences one was expected to have as a result of their use (167).

The "modern era" of specifically mind-altering drugs is often said to have begun with Albert Hofmann's accidental ingestion of LSD-25 in 1943 (77). However, interest in mescaline/peyote was briefly pursued at the turn of the century (48) and in the 1930s (94, 98).

A great flurry of scientific activity with LSD and similarly acting drugs occurred in the 1950s and 1960s, but was just as quickly aborted in the late 1960s as fears of adverse acute and chronic effects of widespread use and abuse began to come to the attention of media and legislators.

Therapeutic and "growth-enhancing" aspects of these substances were widely pursued early on, spurred by such "auto-experimenters" (9) as Aldous Huxley (82), Timothy Leary (97), and Carlos Castaneda (32). A discussion of these aspects of "psychedelic" drug use is beyond the scope of this paper, but interested readers are referred to Grof (65–67), Caldwell (31), Tart (151), Hoffer and Osmond (76), and others (64, 145, 146), as representative selections.

Terminology

The confusion regarding the terminology of this class of drugs, of which LSD-25 is considered the prototype, is reflective of the various orientations respective investigators have taken in approaching them.

For those who have been struck by the primarily perceptual effects of these drugs, the terms *hallucinogenic* or *illusogenic* are used. The similarity between the effects of LSD-like substances and certain psychotic phenomena (a feature that caused them to be employed as potentially producing a "model" of schiz-

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ophrenia) has induced others to label them as *psychotomimetics* or *psychotogens* (39). *Psychedelic*, a term attributed to Osmond (64, p. 8) and defined as "mind-manifesting," although somewhat vague, also carries a less restrictive connotation, and for that reason is the preferred term in this paper. Other words that have been used to describe this class of drugs include *psychodysleptics* (29, p. 4) (mind distortive or mind disruptive), *deliriants*, and *mind-expanding* drugs.

Definition

Psychedelic drugs can be distinguished from other centrally active drugs that can also (under certain conditions) induce perceptual distortions (*e.g.*, anticholinergics), paranoid and other delusions (*e.g.*, amphetamines), and other alterations of cognition, behavior, and affect (*e.g.*, opiates, bromides). They are capable of, when pathological effects are absent or minimal, "reliably inducing or compelling states of altered perception, thought, and feeling that are not (or cannot be) experienced otherwise except in dreams or at times of religious exaltation" (84, pp. 563–564).

Lysergic acid diethylamide-25 is the prototypical psychedelic compound, and was often the active ingredient in most street "psychedelics," during the period in which most of the reference studies were performed, even those labeled "mescaline" or "psilocybin." Unless otherwise mentioned, LSD-25 will be used interchangeably with "psychedelic" in this paper. It is, as are psilocybin, psilocin, diethyltryptamine, and dimethyltryptamine, a member of the indolealkylamine class of drugs. Mescaline (one of the most active ingredients in peyote cactus) is a phenylisopropylamine (84). Phencyclidine (PCP, "hog," "angel's dust," etc.), an arylcyclohexylamine, has attained great currency in the last 10 years, as a common street "psychedelic" in its own right, as well as a substitute/adulterant for other psychedelics. Many current samples of drugs sold as psychedelic, are often found to contain variable amounts of PCP. However, PCP did not become a popularly abused street psychedelic until the mid-1970s, a time by which almost all of the major reports of adverse reactions to LSD had been published. The effects of PCP can be differentiated both pharmacologically and clinically from true psychedelics (84). The interested reader is referred to Lisansky *et al.* (101) for a fuller discussion of these important distinctions.

On the basis of a) subjective effects and neurophysiological actions, b) cross-tolerance between compounds, and c) response to selective antagonists, Martin and Sloan (105) have classified LSD, mescaline, psilocybin, and psilocin as "LSD-like." Differences among the various LSD-like drugs (referred to here as the psychedelics) are primarily a matter of rate of onset, peripheral side effects, duration of action, and intensity of experience. For example, LSD is longer acting (8 to 12 hours) and more potent (average dose of 100 to 500 μg) than mescaline (average dose of 200 to 500 mg and average duration of 6 to 8 hours) and psilocybin or psilocin (average duration of 4 to 12 hours and a dose range of 10 to 50 mg).

Pharmacology

Mechanism of Action

Serotonergic (5-HT) systems (especially in the midbrain raphe nuclei, or neurons projecting from those nuclei) have classically been implicated as the primary source of psychedelics' effects (11, 17, 69, 102). They seem to preferentially inhibit serotonergic cell firing via binding to cell-body or dendritic 5-HT receptors and seem to spare postsynaptic receptors, although this is controversial (83). As serotonin is primarily an inhibitory neurotransmitter, inhibition of these cells by LSD would allow the next neuron in the chain to be freed from inhibition (166).

Dopaminergic systems may also be involved in the central effects of psychedelics. There are preliminary data (41) indicting an agonistic and antagonistic effect of LSD on postsynaptic dopamine receptors.

Carbon-14-labeled LSD given to animals has been found to be maximally concentrated in liver and kidney. Brain concentrations are maximal in hippocampus, basal ganglia, thalamic nuclei, and cerebral cortex. Most of LSD's metabolites are excreted in the feces (127).

Implanted cortical electrodes in humans have shown LSD-associated paroxysmal electrical activity in hippocampal gyri, amygdaloid nuclei, and septum during perceptual changes which are reversed by chlorpromazine (117).

Pharmacological Effects

The effects of an oral dose of LSD (as low as 20 to 25 μg) can be perceived within a few minutes, although with psilocybin and mescaline, onset of initial symptoms is somewhat later (15 to 30 minutes).

Initial physical symptoms are sympathomimetic in nature. These include dilation of the pupils (which retain their reactivity), nausea, flushing, chilliness, increased blood pressure and heart rate, tremor, hyperreflexia, piloerection, weakness, elevated blood temperature, and dizziness (84, 102).

Psychological effects soon follow, and, within 30 to 90 minutes, include feelings of inner tension, affective lability, visual illusions and hallucinations (followed in decreasing frequency of occurrence by auditory and other sense-modalities), blending of sensory modali-

ties (*e.g.*, "seeing sound"—synesthesia), a slowing of subjective time, a sense of ego dissolution/detachment/fragmentation, recollection of long-forgotten memories, and increased sense of meaningfulness of what is being experienced. Religious and mystical insights occasionally occur. As the drug effect wears off, and if the experience has been regarded as generally positive, there is a calm, yet energetic sense of detachment and control. In comparison with the aforementioned positive-valued effects, adverse reactions can occur at any stage of the acute experience and may end up being fairly prolonged.

Between doses of 1 and 16 μg/kg, the intensity of effect is proportionate to the dose (84). The half-life of LSD is about 8 hours in humans (8). Tolerance rapidly develops for psychedelic drugs, and at least 3 to 4 days are necessary for recovery of preexisting sensitivity to a drug of this type.

A withdrawal syndrome does not occur with abupt cessation of LSD-like drugs, and a syndrome of physical dependence is not known. LSD use has been reported to be associated with the occurence of grand mal seizures (52). "Overdoses" of LSD are not directly fatal; however, one suspected case of LSD as a cause of death, in a man whose body was found in a warehouse 1 month after death, has been published (63). An LD_{50} for the human is not known, although an elephant has been killed by a 300-mg intramuscular injection (169). Death occurred in this instance by asphyxiation secondary to laryngospasm.

There are several theoretical frameworks available for understanding the role of LSD in producing psychological effects. None of them are necessarily proposed as absolute, and a perspective that takes into account as many viewpoints as possible will undoubtedly prove most useful.

From a neurobiological point of view, the exact effects of LSD are controversial, but appear to implicate serotonergic function. In the most general sense, inhibited serotonergic function, especially in cortex, raphe, and limbic system, can be presumed to decrease the "filtering" of cognition, perception, and feeling in which serotonergic systems are probably involved. Therefore, mental and physical events are experienced in a novel, less "processed" manner.

Klee (89) has described the effect of LSD on ego functioning (*i.e.*, thought, motility and perception). Body image is disorganized, time sense is profoundly altered, and perceptions of others are distorted, resulting in the sense of "self"-perception being, by and large, lost. Therefore, distinctions between reality and fantasy suffer. Thought processes become dreamlike and concentration becomes difficult. Primary process thinking comes to the fore, and previously neutral words and ideas are responded to as though they were traumatic. The distinction between autonomous and conflictual areas of the ego becomes blurred. From an ego-defense perspective, repression and reaction formation appear most sensitive to the disruptive effects of LSD; projection, denial, introjection, and regression may continue to function effectively. Motorically, some individuals experience impairment in the ability to tolerate tension and delay discharge.

Linton and Langs (99) validated and quantified many similar findings described by Klee. They concluded that "the drug produces an accentuation of thinking by means of images, alterations of self-experience, including feelings of detached self-observation and estrangement, confusion of personal identity, the experiencing of events in terms of implied meanings, loss of boundaries between the self and the environment, drive-dominated thinking, alterations in the distribution of attention cathexis, somatization, and an increase in feelings of passivity, expressed as a subjective loss of control" (99, p. 366).

Tart, in his systems approach to states of consciousness, describes a discrete state of consciousness as a "unique dynamic pattern or configuration of psychological structures, an active system of psychological subsystems" (152, p. 5). This pattern is stabilized by several processes he has described. A change in state of consciousness occurs through the effect of disrupting forces and subsequent action of patterning forces—and then is stabilized by the same processes. Psychedelic drugs are thought to provide disrupting and patterning forces, the effects of which operate in combination with other psychological factors mediated by the operative state of consciousness. Tart feels that LSD causes a highly unstable pattern of psychological structures, characterized by transient formations of patterns that constitute discrete states of consciousness.

Adverse Reactions

It is important to use caution in discussing the concept of adverse reactions to psychedelic drugs. At one extreme are those who believe that the drug-induced state itself is either primarily a pathological one (*i.e.*, a "model psychosis") or that the desire to induce such a state is a function of preexisting personality dysfunction. At the other extreme is the view that even the most disorganized, frightened, dysfunctional, and regressed reactions to psychedelic drugs are necessary/healthy reactions seen in throwing off "straight" society's "shackles" and in reaching a "higher" level of consciousness. The description and/or reporting of adverse reactions to psychedelics is, therefore, subject to some degree of investigators' perspective on the use of these drugs.

It is clearly an adverse reaction when one presents

himself or herself to a (mental) health practitioner with complaints referrable to symptoms induced or exacerbated by psychedelic drugs. It is less clear when changes in behavior, values, or life-style that are brought on, solidified, or symbolized by psychedelic drug use are brought to the attention of care-givers by a concerned other—*e.g.*, friends, co-workers, or relatives. These are cases where sensitive clinical judgment plays as much a role in determining pathological diagnoses as do the salient presenting features of the syndrome.

A large number of methodological issues need to be addressed before beginning an analysis of available reports of adverse reactions. I will attempt to address certain of the most salient features before discussing these studies.

I have excluded from analysis reports that include less than 10 subjects. Many of these are case reports of a few individuals. Some are in-depth analyses of these subjects, often from a psychodynamic and genetic perspective. Although heuristically of value, they are difficult to evaluate from the viewpoint of developing testable hypotheses.

The remaining studies, I believe, can be divided into four general categories:

a) Studies with patients seen in an acute treatment facility (emergency room or inpatient unit) because of symptoms thought to be related to LSD.
b) Studies where questionnaires were mailed to clinicians and/or researchers, polling their experiences with subjects in therapeutic, experimental, and uncontrolled settings.
c) Follow-up studies of subjects who took LSD in experimental, therapeutic, or uncontrolled settings.
d) Studies where subjects were given LSD in a controlled environment and then responses evaluated immediately thereafter.

Table 1 is organized around this categorization of relevant studies.

One of the most confounding aspects of almost all studies of either acute or chronic effects of LSD is their lack of pre-LSD data. The role of LSD in producing "LSD psychoses," brain damage, long-lasting personality change, and flashbacks is difficult, if not impossible to discern without pre-LSD values for the dependent variables.

Table 1 lists the features I believe to be important to address in studies of adverse reactions to psychedelics. They would be included in what might be called the "ideal" study on adverse reactions to psychedelics.

Sample size: Should include ratio of male to female subjects.

Case-finding methods: This will obviously have an effect on the population studies. For example, subjects volunteering to be studied will often have different character traits, and possibly pathology, from those refusing to do so.

Age range and average age should be specified, as reports often emphasize the increased susceptibility of younger subjects to adverse reactions (*e.g.*, 77).

The *definition* of an adverse reaction needs to be specified, as more or less liberal definitions will have related effects on the frequency of their occurrence. It would be ideal to test inter-rater reliability and validity of the definitions, as well.

Source of the drug is self-evident, as adulterants of "psychedelics" can be quite psychotoxic.

The *number of drug exposures* (and, if available, the dosage taken) can indicate total cumulative exposure to psychedelics, a factor that appears to be quite important in several regards (*e.g.*, frequency of adverse reactions, long term psychological effects, flashbacks, etc.).

The *time elapsed* between the last trip and the date of being interviewed or tested is important, both in terms of retrospective alteration of the subject's memory of the experience (100), as well as the presence or absence of acute drug effects.

Study methods can vary widely and range from simple direct clinical observations, to detailed neurochemical studies. Other methods have included in-depth clinical interviews, questionnaires, paper and pencil psychological testing, and interviewing subjects' therapists and families.

The *setting* (*i.e.*, place and people present) needs to be specified. Early reports of adverse reactions occurring in controlled supervised settings were marked by a very low frequency of occurrence (34), and whether or not the setting was unsupervised could have a powerful effect on the frequency and nature of adverse reactions.

Premorbid population characteristics include a) *legal history* as an indicator of sociopathy, drug abuse, and object relations in general; b) *previous psychiatric history*, either in the subject or in the family of origin. This is particularly germane to addressing the questions of preingestion psychopathology and whether or not a genetic/biological "diathesis" exists in selected individuals to develop adverse reactions (*e.g.*, 61); c) *other drug use* is obviously relevant, particularly if one is to assign an etiological role to LSD is causing aberrant behavior, brain damage, or personal distress.

Motivation for psychedelic drug use has been shown by many groups to be related to outcome of the drug experience and relates both to premorbid characteristics of the subject, as well as to the setting in which he/she would most likely be taking the drug (*e.g.*, 56).

The presence of *placebo*, whether (preferably) an active one (*e.g.*, stimulant drug) or an inactive one

(*e.g.*, saline) in controlled experiments would add to the validity of a particular study. The presence of appropriately matched *controls* would also provide helpful comparison data.

The presence or absence of *pre-LSD data* as previously discussed, helps differentiate the etiological *vs.* associative relationship between LSD use and relevant findings.

Presence or absence of *follow-up* and its duration need to be specified, especially in terms of studying long term effects of these drugs. The re-emergence, disappearance, or prolongation of symptoms will determine, to a large extent, the degree of disability incurred by the use of the psychedelics.

The *incidence* of adverse reactions obviously is determined by the definition of these reactions, and the poulation being studied. It is clear that, among inpatients admitted because of LSD reactions, 100 per cent of these individuals have had an "adverse reaction." Likewise, the incidence of transient painful, anxious, and depressed experiences at *some* time during most LSD experiences appears to be quite common. Most studies have defined adverse reactions operationally, *i.e.*, those reactions that have come to the attention of individuals in the (mental) health field.

Keeping these points in mind, one can begin sorting through the voluminous and variegated literature on adverse reactions to psychedelic drugs (33, 35–37, 137). Table 1 is meant to aid in analyzing various reports, particularly in terms of the absence or presence of these parameters being specified.

Classification

The *temporal relationship* between the ingestion of a psychedelic drug and subsequent dysphoric or maladaptive symptoms is probably the most helpful means of beginning a classification of adverse reactions, *i.e.*, on a *continuum* from *acute* to *chronic*. Between these two ends of the spectrum would be the phenomena of *delayed* reactions (*e.g.*, a panic reaction or psychosis occurring after an asymptomatic interval) (70), *intermittent* reactions (such as "flashbacks"), and the "LSD psychoses" (including the *psychedelic-precipitated* major functional disorders).

The most common adverse reaction is a temporary (less than 24 hours) episode of panic—the "bad trip" (159–162). Symptoms include frightening illusions/hallucinations (usually visual and/or auditory); overwhelming anxiety to the point of panic; aggression with possible violent acting-out behavior; depression with suicidal ideations, gestures, or attempts; confusion; and fearfulness to the point of paranoid delusions.

Reactions that are prolonged (days to months) and/or require hospitalization, are often referred to as "LSD psychoses," and include a heterogenous population and group of symptoms (13, 18, 42, 44, 57, 128, 129, 131, 141, 161–163). Although there are no hard and fast rules, some trends have been noted in retrospective analyses of these patients. There is a tendency for people with poorer premorbid adjustment, a history of psychiatric illness and/or treatment, a greater number of exposures to psychedelic drugs (and correlatively, a greater average total cumulative dosage taken over time), drug-taking in an unsupervised setting, a history of polydrug abuse, and self-therapeutic and/or peer-pressure-submission motive (122) for drug use, to suffer these complications.

In spite of the impressive degree of prior problems noted in many of these patients, there are occasional reports of severe and prolonged reactions occurring in basically well adjusted individuals (70). In the same vein, there are many instances of fairly poorly adapted individuals who suffer *no* ill effects from repeated psychedelic drug use. In fact, it has been hypothesized that some schizophrenics do not suffer adverse reactions because of their familiarity with such acute altered states, and their ability to let them run their course (59). Another possibility is that these individuals may be "protected" by possible "down-regulation" of the receptors for LSD, by the (over-) production of some endogenous compound. *Individual* prediction of adverse reactions, therefore, is quite difficult. However, some well designed prospective studies have shown that particular individuals are especially prone to adverse acute reactions (see below).

Symptomatically, these patients present with a wide variety of symptoms, belying the great variety of their premorbid features (120). Formal thought disorder, hallucinations, illusions, violence, paranoid and other delusions, depression, regression, emotional lability, bizarre behavior, insomnia, hypomania, depersonalization, dissociative states (43), confusion, and apathy can be seen.

Bowers *et al.* analyzed some neurohumoral features of LSD-induced *vs.* non-LSD-induced psychoses, and found that the CSF of the former group gave evidence of decreased central 5-hydroxyindoleacetic acid (a metabolite of serotonin) formation, a finding that persisted during phenothiazine treatment. Homovanillic acid (a dopamine metabolite) in the CSF did not show a difference in levels between these two groups (24).

Infrequently reported, but receiving great publicity, were the articles on homicides that occurred in association with LSD use. Knudsen (93) described a young woman with a long history of polydrug and alcohol abuse, sexual masochism, sociopathy, and a major depression treated with electroconvulsive therapy (ECT), who murdered her sexual partner 3 days after the fifth of a series of LSD psychotherapy sessions.

TABLE 1

Studies of Adverse Reactions to LSD

Study	N (m,f)[a]	Age (Avg.)	Case-Finding Method	Drug Source	Dose (No. exp.)	Other Drugs	Setting	Controls (Placebo)	Pre-LSD Data
Acute LSD Reactions									
Frosch (56, 57)	12 (7,5)	18–32 (23)	Hospitalized for "LSD reaction"	N.M.	200–400 μg (1–10)	Polydrug, alcohol abuse in 11	Unc.	None (None)	None
Tietz (157)	49 (37,12)	n.s. (<25)	Hospitalized for "LSD reaction"	N.M.	100–2500 μg (n.s.)	Polydrug, alcohol abuse in "most"	Unc.	Yes (None)	None
Ungerleider (161, 162)	70 (53,17)	16–36 (21)	E.R. visit with LSD mentioned in diagnosis	N.M.	n.s. (1–200)	Polydrug abuse in 40%	Unc.	"Cult" users of LSD (None)	None
Robbins (128, 129)	22 (11,11)	15–43 (21)	Hospitalized for "LSD reaction"	N.M.	n.s. (1–100+)	Polydrug abuse "typical"	Unc.	None (None)	None
Blumenfield (22, 21)	25 (18,7)	n.s. (22)	E.R. visit for "LSD reaction"	N.M.	n.s. (1–10+)	Polydrug, alcohol abuse in most	Unc.	None (None)	None
Frosch (55)	23 (14,9)	16–33 (22)	Hospitalized for "LSD reaction"	N.M.	400–600 μg (56% with 1–5)	Polydrug abuse in most	Unc.	Yes (None)	None
Baker (13)	67 (34,33)	n.s. (n.s.)	Hospitalized for drug abuse	N.M.	n.s. (n.s.)	Polydrug abuse in 26	Unc.	None (None)	None
Dewhurst (44)	19 (13,6)	18–37 (24)	Hospitalized for "LSD reaction"	N.M.	n.s. (8-once 11-chronic)	Other drug abuse in 14	3 Med. 16 Unc.	None (None)	None
Forrest (54)	60[b] (43,14)	n.s. (20)	Hospitalized for "LSD reaction"	N.M.	n.s. (n.s.)	Previous drug use in 72%		None (None)	None
Questionnaire Studies									
Cohen (34)	5000 (n.s.)	n.s. (n.s.)	44/62 questionnaires returned	M.	25–1500 μg (1–80)	n.s.	Variable	n.s. (n.s.)	n.s.
Ungerleider (163)	2000 (m > f)	15–30 (n.s.)	1580/2700 questionnaires returned	n.s.	n.s. (n.s.)	n.s.	n.s.	n.s. (n.s.)	n.s.
Malleson (103)	4470 (n.s.)	n.s. (n.s.)	73/74 questionnaires returned	M.	25–1500 μg (49,000)	n.s.	Variable	n.s. (n.s.)	n.s.
Follow-up Studies									
Ditman (45)	74 (n.s.)	n.s. (n.s.)	Volunteers, pts.	M.	100 μg (1)	50% alcoholic	Med.	None (None)	None
Savage (136)	93/ (n.s.) 74 (48,26)	n.s. 22–67 (37)	Pt. volunteers	M. M.	200–600 μg[c] (1)	n.s. n.s.	Med. Med.	None/(None) None/(None)	None None
Kleber (87, 88)	21 (21,0)	18–24 (n.s.)	Volunteers	N.M.	n.s. (1–20)	Marijuana in 9	Unc.	None (None)	None
Bhattacharya (19)	581 (n.s.)	n.s. (n.s.)	Pts.	M.	n.s. (2742)	n.s.	Med.	n.s. (n.s.)	n.s.
Shagass (139)	20 (13,7)	16–36 (24)	Inpt. volunteers	M.	2.5 μg/kg i.v. (1)	n.s.	Med.	Yes (Amphetamine)	Psychiatric dx's
Ditman (46)	116 (98,18)	15–47 (n.s.)	Volunteers, pts. treated for LSD reactions	M., N.M.	75–1500 μg (1–100+)	Other drug abuse in 80%	Unc.	None (None)	None
Barron (15)	20 (14,6)	16–31 (22)	Volunteers	N.M.	100–150 μg (8–250)	Polydrug abuse in all	Unc.	None (None)	None
McGlothlin (113)	247 (164,83)	n.s. (34)	Volunteers, pts.	M., N.M.	25–700 μg (1–20)	Some used multiple drugs	Variable	Yes (None)	n.s.
Naditch (120, 121, 123)	483 (483,0)	n.s. (21)	Volunteers	N.M.	n.s. (1–100+)	Marijuana in 92%	Unc.	None (None)	None
Immediate Observation Studies									
Pauk (125)	14 (8,6)	19–37 (23)	Inpt. volunteers	M.	15–500 μg (3–5)	n.s.	Med.	None (None)	Psychiatric dx's
Anastasopoulos (10)	97 (n.s.)	n.s. (n.s.)	Relatives of schizophrenics	M.	1–15 μg/kg p.o. (1)	n.s.	Med.	Yes (None)	Nonsymptomatic
Fink (50)	65 (n.s.)	20–53 (36)	Inpt. volunteers	M.	60–250 μg (1–15)	Concurrent psychotropics	Med.	None (Saline)	Psychotic dx's
Langs (96)	50 (50,0)	21–42 (n.s)	Volunteers	M.	100 μg (1)	n.s.	Med.	None (Tap water)	Extensive

[a] Abbreviations: m, male; f, female; Avg., average; No. exp., number of exposures; Psych Hx, past personal psychiatric history; Fam Hx, family psychiatric history; adv. rxn., adverse reaction; N.M., nonmedical; Unc., uncontrolled; n.s., not specified; sx, symptom; E.R., emergency room; halluc's, hallucinations; pt., patient; Med., medical setting; M., medical; n.a., not applicable; Inpt., inpatient; i.v., intravenously; dx, diagnosis.

[b] Some patients admitted more than once.

[c] Plus 300 to 400 mg of mescaline.

Time Lag	Study Method	Population	Legal Hx	Psych Hx (Fam Hx)	Motivation	Definition of adv. rxn.	Incidence	Follow-up	Comments
					Acute LSD Reactions				
1–90 days	Clinical observation	White, unmarried	n.s.	5 psychotic (n.s.)	Pleasure	Panic, sx recurrence, psychosis	0.4% of admissions	n.s.	3 psychotics with Hx of psychosis
1–90 days	Clinical observation; testing	Low socioeconomic status	n.s.	None (n.s.)	n.s.	Panic, sx recurrence, psychosis	n.s.	1–5 mos for 17	67% with extended psychosis
1–42 days	Clinical observation; chart review	33% unemployed	14%	37%; 45% no data (n.s.)	n.s.	Seen in E.R.	n.s.	n.s.	25% hospitalized; 68% needed >1 mo of treatment
1 day to 12 mos	Clinical observation	White, married	n.s.	3 psychotic (n.s.)	"Kicks," self-help	Panic, sx recurrence, psychosis	n.s.	n.s.	3/8 with psychosis previously ill
1 day for 14	Clinical observation; chart review	26% unemployed	40%	72% (n.s.)	Self-help, curiosity	Suicidal, anxiety, confusions, halluc's	0.3% of admissions	n.s.	Psych Hx almost always preceded LSD use
n.s.	Clinical observation	Upper and middle class	n.s.	n.s. (n.s.)	Pleasure	Panic, sx recurrence, psychosis	n.s.	n.s.	Younger pts. over-represented
n.s.	Clinical observation	n.s.	n.s.	n.s. (n.s.)	n.s.	Psychosis, suicidal, aggressive	n.s.	n.s.	LSD relation to sx's unclear in 36
"Soon after" for 8	Clinical observation	Above avg. IQs; students	n.s.	8 (n.s.)	n.s.	Psychosis	n.s.	n.s.	No residual problems at discharge
n.s.	Clinical observation	40% unemployed	69%	83% (n.s.)	n.s.	Needing hospitalization	n.s.	n.s.	16 needed psychiatric help
					Questionnaire Studies				
n.s.	Clinical observation	n.s.	n.s.	Common in adv. rxn. (n.s.)	Volunteers, patients	Psychosis, suicidal, agitation	See Comments	n.s.	Psychosis: 0.8–1.8/1000; suicide attempts: 0–1.2/1000
n.s.	Clinical observation	n.s.	n.s.	Many in adv. rxn. (n.s.)	n.s.	Arbitrary	See Comments	n.s.	27% of respondents had seen "adverse reactions"
n.s.	Clinical observation	n.s.	n.s.	n.s. (n.s.)	n.s.	Suicidal psychosis	See Comments	n.s.	Psychosis: 9/1000 (⅓ previously ill); suicide: 0.7/1000
					Follow-up Studies				
n.a.	Questionnaires	50% professional	n.s.	50% alcoholic (n.s.)	Volunteers	Anxiety, depression, headaches	15%	2 yrs	Symptoms lasted 1–21 days
n.a.	Interviews;	n.s.	n.s.	100% (n.s.)	Therapy	"Felt harmed,"	1/167	Variable	80% improved
n.a.	questionnaires	n.s.	n.s.	100% (n.s.)	Therapy	suicide, psychosis	1/167	2–6 mos	
n.a.	Interviews	Students; top half of class	n.s.	11 (n.s.)	Curiosity, self-help, pressure	Panic, sx recurrence, flashbacks	24%	Variable	"Stable" group with no adv. rxns.
n.s.	n.s.	n.s.	n.s.	100% (n.s.)	n.s.	n.s.	None	n.s.	All with transient emotional disturbance
n.a.	Interviews	n.s.	Most	100% (n.s.)	Therapy	n.s.	None	1 yr	Psychopaths often improved
n.s.	Interviews; testing	n.s.	n.s.	n.s. (n.s.)	Volunteers	Needing treatment	None	n.s.	Polydrug abusers did most poorly
n.s.	Interviews; testing	16 working or in school	n.s.	None (n.s.)	Curiosity, insight, escape	Panic over several hours	15/20 11/20 with flashbacks	n.s.	Marginal adaptation predated LSD use
n.a.	Interviews; testing	n.s.	n.s.	123 (n.s.)	Therapy, insight, pleasure	Psychosis, suicidal	1 psychosis; 7 suicides	10 yrs	6/7 suicides were 2 yrs after last "trip"
n.s.	Questionnaires	65% students	n.s.	n.s. (n.s.)	Self-help, pressure, pleasure	Fear of psychosis	n.s.	n.s.	Set, frequency, related to adv. rxns.
					Immediate Observation Studies				
Immediate	Clinical observation	n.s.	n.s.	100% (n.s.)	Volunteers	Psychosis	50%	n.s.	Object of study was to induce psychosis
Immediate	Clinical observation	n.s.	n.s.	None (Schizophrenic)	Volunteers	Paranoia, depression	37/97	6 weeks	Adv. rxns. in normals not specified
Immediate	Clinical observation	n.s.	n.s.	100% (n.s.)	Volunteers	Increased sx's, confusion	2%	3 mos	"Classic" schizophrenics did relatively well
Immediate	Clinical observation; testing	Actors	n.s.	No overt psychosis (n.s.)	Volunteers	Paranoia during study	27%	Several days	Primitive character disorders did poorly

Barter and Reite (16) described the case of a young chronic paranoid schizophrenic male who killed his mother-in-law. He had taken small quantities of LSD in the past, his last experience having been a month before the murder. In the interim, he had been drinking large quantities of alcohol and abusing barbiturates. The same authors described another young man with no previous drug abuse or psychiatric history who murdered a "comparative stranger during an argument" (16, p. 533); the details of both his relationship to the stranger and the nature of the argument are not included in the report. He had also been drinking that night and remembered nothing of the incident.

Klepfisz and Racy (92) described a young man with a 3-year history of polydrug abuse, including amphetamines and cocaine, who killed a girlfriend 2 days after an LSD experience.

Reich and Hepps (126) described a young man with paranoid and borderline character pathology who killed a stranger after 8 days of sleep deprivation, round-the-world travel, and psychosis, following an LSD experience. He had a history of depression and polydrug abuse.

These cases, except perhaps for the Reich and Hepps example, do not clearly implicate LSD in the murders described. The role of other drugs and alcohol, as well as chronic psychosis, seem at least equally relevant. In the Reich and Hepps case, a temporal relationship between LSD use and psychosis was apparent, but as will be discussed later, the *specific* nature of LSD as having precipitated the psychosis, as opposed to other drugs, jet travel, or the cumulative effects of transient, unsatisfactory relationships in a previously marginally adapted individual, is difficult to determine.

Reports of suicide have been occasionally described in the literature (86), and are most often included in large case analyses. Data regarding the role of LSD in these individuals' self-destructive behavior is difficult to glean from these reports, but McGlothlin *et al.* (115), for example, described a weak temporal relationship between LSD use and suicidal actions. What is missing in these reports, but most germane to them, is information regarding premorbid symptomatology and suicide attempts, other drug alcohol abuse, and the nature of the situation in which LSD was taken.

Self-inflicted ocular injuries, including self-enucleation (130, 155) or retinal burns from staring at the sun (58), have been reported infrequently. These injuries were described in individuals for whom little or no premorbid and/or psychiatric follow-up data are available, and what was described demonstrated poor adjustment in the years before the self-inflicted injuries.

Major "functional" psychoses vs. "LSD psychoses." A diagnostic issue dealt with explicitly in only a few papers is that of *LSD-precipitated* major functional illnesses, *e.g.*, affective disorders or schizophrenia. In other words, many of these so-called LSD psychoses could be other illnesses that were triggered by the stress of a traumatic psychedelic drug experience. Some of the same methodological issues described earlier affect these studies, but they are, on the average, better controlled, with more family and past psychiatric history available for comparison.

Hensala *et al.* (74) compared LSD-using and non-LSD-using psychiatric inpatients. They found that this group of patients was generally of a younger age and contained more characterologically disordered individuals than the non-LSD-using group. Patients with specific diagnoses with or without LSD histories were not compared. Based on their observations, they concluded that LSD was basically just another drug of abuse in a population of frequently hospitalized individuals in the San Francisco area, and that it was unlikely that psychedelic use could be deemed etiological in the development of their psychiatric disorders.

Roy (133), Breakey *et al.* (28), and Vardy and Kay (165) have attempted to relate LSD use to the onset and development of a schizophrenia-like syndrome. A few comments regarding this conceptual framework seem in order, before their findings are discussed. The major factor here is that of choosing schizophrenia, or in the Vardy and Kay study, schizophreniform disorders, as the comparison group. There is an implication here that LSD psychoses are comparable, phenomenologically, to schizophrenia-like disorders, and that LSD can "cause" the development of such disorders. The multiplicity of symptoms and syndromes described in the "adverse reaction" literature should make it clear that LSD can cause a number of reactions that can last for any amount of time—from minutes to, possibly, years. I believe that what is being studied here is the question of the potential role of LSD in *accelerating* or *precipitating* the onset of an illness that was "programmed" to develop ultimately in a particular individual—in a manner comparable to the major physical or emotional stress that often precipitates a bona fide myocardial infarction in an individual with advanced coronary atherosclerosis. The stress did not *cause* the heart disease; it was only the stimulus that accelerated the inexorable process to manifest illness.

In looking at the relevant studies, Breakey *et al.* (28) found that schizophrenics who "used drugs" had a earlier onset of symptoms and hospitalization than non-drug-using schizophrenics, and had possibly better premorbid personalities than non-drug-using patients (although Vardy and Kay have challenged this analysis of Breakey's data [165]).

Bowers (23) compared 12 first-admission patients with psychoses related to LSD use, requiring hospitalization and phenothiazines, to 26 patients hospitalized and treated with phenothiazines with no history of drug use. Six of these controls had been previously hospitalized. Drug-induced psychotic patients were found to have better premorbid histories and prognostic indicators than the nondrug groups. There was no difference in rates of family history of psychiatric illness. However, several issues flaw this study. One is the polydrug-abusing nature of the "LSD-induced" psychotic patients, compared to the controls. The role of LSD, therefore, in causing or precipitating these symptomatic disorders, is open to dispute. The other is the lack of an adequate comparison control group, *i.e.*, the controls were specified only as "psychotic," and did not necessarily match the LSD group in either symptoms or diagnostic classification. A follow-up study of the LSD patients occurred between 2 and 6 years later (25). One half did well and one half did poorly, although the lack of control group for a follow-up in a similarly symptomatic control group makes interpretation of the data difficult.

Roy (133), in a somewhat different design, compared chronic schizophrenic patients (diagnosed according to DSM-III criteria) who had used LSD within the week preceding hospitalization, and found no differences in age of symptom onset or hospitalization compared to patients without a history of illicit drug use.

Vardy and Kay, in an elegant study with a 3- to 5-year follow-up period, demonstrated that patients hospitalized for a schizophrenic picture that developed within 2 weeks of LSD use (patients with other diagnoses were explicitly excluded from comparisons with non-drug-using schizophrenics) were "fundamentally similar to schizophrenics in geneology, phenomenology, and course of illness" (165, p. 877). Premorbid adjustment, age of onset of symptoms and hospitalization, family history of psychosis or suicide, and most cognitive features were also equal between groups. Family histories of alcohol abuse were markedly greater in the LSD group.

I believe that these data, taken as a whole, limited as they are in terms of comparing subgroups (*i.e.*, LSD-using *vs.* non-LSD-using) of "schizophrenia-like" disorders, point toward, at the most, a possible precipitatory role in the development of these disorders, in a nonspecific and not etiologically related manner.

Most reports have stressed the similarities between LSD-induced psychotic states and schizophrenia, and therefore compare "functional" schizophrenia to LSD-induced states that resemble schizophrenia. However, there are data to support a relationship between affective illness and LSD-induced psychoses. Lake *et al.* (95) described a case of mania precipitated by LSD; Muller (119) and Dewhurst and Hatrick (44) described the efficacy of ECT in LSD psychoses; cases have also been treated with lithium (80). Bowers (26), in his discussion of the role of serotonin in psychosis, emphasizes the fact that "good prognosis" schizophrenics and LSD-induced psychoses have similar CSF levels of the serotonin metabolite 5-hydroxyindole-acetic acid. The fact that many of the so-called "good prognosis" schizophrenics are either often rediagnosed as affectively ill, and/or will often have family histories of affective illness, lends support to the contention that the relationship between relatively long-lasting psychedelic drug-induced psychoses and affective disorders deserves further study (85).

Prospective studies of acute adverse reactions. A unique group of studies deserves mention: those of Klee and Weintraub (90), Pauk and Shagass (125), Anastasopoulos and Photiades (10), Fink *et al.* (50), and Langs and Barr (96). These are representative of the small number of studies that have looked at individuals *before* administration of LSD, in order more confidently to state relationships between adverse drug reactions and preexisting characteristics. Three studies of somewhat similar design are those of Klee and Weintraub, Pauk and Shagass, and Langs and Barr. Here, individuals were pretested with various instruments before being given LSD. Klee and Weintraub found that individuals with a fear of closeness of same-sex others and a strong tendency to use projection as a major defense mechanism were regularly those who developed a paranoid reaction *during* the LSD state, lasting, at the most, 24 hours.

Pauk and Shagass found that individuals who responded to low doses of LSD with disorganization of their Bender-Gestalt tests were most likely to develop "psychotic" states after higher dose LSD ingestion. They thought that this test was helpful in indicating "ego-function" impairment by LSD.

Langs and Barr applied multiple psychological tests, interviews, and questionnaires to a group of "normals." Those who had short-lived (less than 24 hours) paranoid reactions were found to be "more anxious, manipulative, hostile with conflicts about aggression, depressed and self-punitive: to feel physically impaired, prone to a thought-disorder and confused in their identities; and likely to use projection as a defense" (96, p. 168). These three studies all point toward the possible development of more effective personality screening tools for individuals being considered for LSD experiments.

Anastasopoulos and Photiades administered LSD to previously "asymptomatic" relatives of schizophrenics, although more sophisticated studies were

not performed. A very high percentage of these individuals had adverse reactions lasting up to 6 weeks. Siblings of schizophrenics showed adverse reactions to LSD only in cases where one or both parents showed decompensation. The significance of these findings is clear, and may relate to the often found relatively high rate of familial mental illness in the so-called LSD psychoses.

Fink *et al.* gave LSD to 65 psychotic subjects and noted a 2 per cent incidence of prolonged adverse reactions, which were described as basically exacerbations of preexisting psychopathology with accompanying signs of a confusional delirium. Chlorpromazine, later introduced as a prophylactic agent at the end of subsequent LSD studies, was successful in preventing any further prolonged adverse reactions from occurring. These data are particularly interesting from the perspective of the high incidence of premorbid psychopathology of many of the "LSD casualties" reported in the literature on unsupervised use of the drug.

A Note on the Etiology of Adverse Reactions

What are the etiologies of the above described adverse reactions to psychedelic drugs? I believe that this question should be addressed from several perspectives, with multiple levels of interaction. The heterogeneity of responses to LSD make generalizations about responsiveness to the drug impossible. Theoretical frameworks explaining their effects have been proposed in terms of biological, psychological, and systems approaches. The interplay of these factors, combined with the effect of the drug and particular setting, result in one particular individual's "LSD experience."

Constitutional predispositions have been described, wherein family histories of major functional illnesses are often associated with poor outcome in uncontrolled settings. A past personal history of previous psychiatric treatment and/or the presence of particular characterological pathology have also been shown to be associated with adverse reactions.

My feeling is that, in a particularly predisposed individual (be it genetic, motivational, or characterological), the flood of images, drives, feelings, and perceptions, occurring in a setting where the person has not been either adequately prepared and/or supported, a breakdown in the normal means of processing internally and externally derived information occurs, with associated reactions, depending on one's ability to tolerate such experiences. (I will not address the issue of mystical experiences obtained during the breakdown of normal mental processes occurring during LSD intoxication, except to say that they do occur [*e.g.*, 106] and appear to be most likely subject to the same formal rules of operation and development as adverse reactions [*i.e.*, constitutional, genetic, characterological, preparation, motivation, etc.].)

Now, the duration of such an experience may last from minutes to hours to weeks or longer. The duration appears to be dependent on several variables, including, most likely, a familial or personal predisposition to the major functional psychoses (158). Total cumulative exposure may also have direct bearing, especially as described by Abraham (3) and Glass and Bowers (60).

Chronic effects. The *chronic* adverse reactions to psychedelic drugs described in the literature are also composed of a fairly heterogenous population and group of symptoms (37, 51, 87). Studies of chronic effects of LSD can be divided into two categories: 1) those involving long-lasting psychological and personality effects of LSD use in patients and nonpatients (including experimental subjects); and 2) those involving measures of organicity in individuals with repeated use.

The study of Blacker *et al.* (20) focused on 21 chronic LSD-using volunteer nonpatients, a group they referred to as "acidheads." Predrug measures of personality or other variables were not available. These individuals were described as "having profound non-aggressive attitudes, magic-mystical beliefs, relatively intact interpersonal relationships, and cognitive abilities that are more similar to individuals usually termed eccentric than to individuals diagnosed as schizophrenic" (20, p. 349). However, whether these beliefs predated the LSD use could not be determined.

McGlothlin *et al.* (115) studied changes in personality, attitude, values, aesthetic interest, and performance resulting from LSD administration in normals who had participated in a series of three well controlled LSD sessions. Follow-up on this group was at 2 weeks and 6 months. Galvanic skin response dropped in three individuals at 6-month follow-up, indicating an elevated ability to manage stressful situations. In spite of subjective feelings that subjects had become more creative, aesthetically appreciative, and less defensive, objective data did not particularly support these perceptions.

Axelrod and Kessel (12) administered the Rorschach to three groups of 10 individuals described as having taken LSD more than 30 times in a 3-year period, one to five times in that same period, or never. Significantly more "ego disturbance" was found in the LSD-using groups compared to nonusers. However, this study suffers from lack of premorbid testing, and control issues regarding use of other drugs.

Salzman *et al.* (135) compared individuals who had discontinued taking psychedelic drugs 6 months before being studied with those still taking psychedelics. In-

dividuals were studied by a variety of paper and pencil psychological tests. Except for elevated risk-taking behavior among continuers, the two populations could not be differentiated.

McGlothlin and Arnold (113) performed a 10-year follow-up on 247 individuals who had received LSD in an experimental ($N = 123$) or psychotherapeutic setting ($N = 124$) with careful medical supervision. The groups were controlled by comparing patients who took LSD on their therapists' initiative, with patients of the same therapists who did not use LSD in therapy. The sample was further distinguished by a group who continued using psychedelics after the experiments or therapy were over. Patients who had LSD in a therapeutic setting initiated by their therapists, showed no greater changes on individual variables than the non-drug-experienced control group over a comparable time period. The LSD continuers did show appreciable differences in a number of areas relating to measures of personality, values, beliefs, and attitudes. The nonmedical continuers of LSD also used more drugs and alcohol in general than the two other groups. They also engaged in and were interested in nonpharmacological ways of altering consciousness. The authors thought that perhaps a particular type of individual was drawn to LSD, which then acted in a catalytic manner to reinforce the individuals' interest in altered states of consciousness. Interestingly, LSD use, by the "continuing" sample, declined with time.

The question of organic deficits in users of LSD has been addressed by several investigators. Blacker *et al.* (20) used cognitive, perceptual, and EEG tests in their population of "acidheads." The incidence of abnormal baseline EEGs was thought to be no greater than might have been expected in a non-drug-using group of young adults. Computer analyses of EEG data showed increased energy in four specific frequency bands in the LSD group over the left occipital area as compared to LSD nonusers. The significance was unknown. Visual evoked potential studies showed increased sensitivity in a few instances in the LSD group. Auditory evoked potential responses were similar to normals, and cognitive studies revealed some slower response times as compared to normals. The authors could not conclude that LSD produced any form of CNS damage. As in the description of the characterological analysis part of this study previously described, these findings are limited by a lack of premorbid studies and control for other drug use.

Accord (6) studied 40 white males, with an average age of 20 and a mean educational level of 12 years. Intelligence tests were thought to be an average. Neuropsychological testing was performed using the Indiana Neuropsychological Battery. Thirty-two subjects performed in the "brain-damaged range" on at least one test, 18 on at least two, and five on all three. No gross cerebral pathology was noted. This study, however, is flawed by lack of controls, premorbid testing, and consideration of other drug use.

In a later publication, Accord and Barker (7) studied in the same manner, 15 patients with a history of psychedelic use. In this study an age-matched population of non-psychedelic-using patients was obtained. Psychedelic-using patients scored lower than non-drug-using patients. In one of the three tests, the results of psychedelic users fell below cutoff scores for non-brain-damaged individuals. However, these norms were established for individuals nearly twice as old as the subjects of the study. This study is also flawed by lack of predrug use measures and poor control for other drugs.

Culver and King (40) performed a retrospective study of 42 college seniors, divided into three equal groups of 1) controls, 2) marijuana/hashish users, and 3) LSD users (all of whom also used cannabis products). Other drug use was carefully controlled for, except alcohol. Groups were matched by verbal and math Scholastic Achievement Test (SAT) scores and freshman MMPI profiles. Grade point averages among groups showed no differences. A neuropsychological test battery was administered, including the Halstead Battery, Wechsler Adult Intelligence Scale, Reitan's Trail-Making Test, and several others. The only abnormality found in the LSD group was a poorer performance on the Trail-Making Tests (although scores were well within the normal range). The degree of LSD use did not correlate with subjects' performance. Alcohol use was greater in both LSD and cannabis users, but the abnormal results of the Trail-Making Test persisted after a statistical adjustment for alcohol consumption was made. The authors were unclear as to the significance of the relatively low Trail-Making Test performance and thought that lack of pre-drug use testing could not rule out the existence of this finding as a "premorbid" characteristic.

Cohen and Edwards (38) compared 30 LSD-using nonpatient volunteers (equal numbers of men and women) to 30 age-, sex-, education-, IQ-, and socioeconomic status-matched controls. Members of the LSD group had taken illicit LSD in uncontrolled settings at least 50 times, and had used very large quantities of other illicit drugs as well. Glue-sniffers were excluded, and individuals were asked to refrain from taking drugs for 48 hours before testing. The drug-taking group was found to perform significantly worse on Trail-Making Test A and the visual spatial orientation test of the Halstead-Reitan Battery. Both groups performed equally well on all other subtests, and on the Raven Progressive Matrices. There was no pre-drug use data, nor could the effect of LSD per se

be specified, particularly with the quantities of other drugs abused.

McGlothin *et al.* (114) studied 16 individuals with an average age of 40. All were white, two thirds were male, and all but one had a college education. Ten had received LSD as psychotherapy subjects and six as experimental subjects. Average number of doses was 20, and 13 had used LSD outside of a medical setting. Combined number of exposures in medical and nonmedical settings was 75. Most had not taken LSD for 1 year before testing. A control group, matched for age, sex, education, psychotherapy, occupation, and use of marijuana, was also studied. A large number of tests were administered, including the Trail-Making A Test and the Spatial-Orientation Test, these two tests having demonstrated performance abnormalities by LSD users in Cohen and Edwards' study. This group found only one subtest to be performed in a statistically significant poorer manner by the LSD group, and this test (Halstead's Category Test) was still performed within the normal range. No correlation was shown between degree of LSD use and scores on this subtest. In spite of this being a generally much-better-designed protocol, it still lacks the crucial factor of pre-drug use testing.

Wright and Hogan (170) studied a group of 20 frequent LSD users (five women and 15 men) with a mean age of 20 and a mean duration of LSD use of 12 months. The average number of LSD experiences was 30. Approximately 1 month was the average time from last using LSD. Twenty age-, sex-, education-, and intelligence-matched non-drug users were used as controls. The Halstead-Reitan Neuropsychological Test Battery and the Halstead-Wepman Aphasia Test were administered to both groups. No significant differences between groups could be found. Here again, pre-drug use testing, and control for other drug and alcohol use were not performed.

An unusual chronic adverse reaction was recently described by Abraham (1). Forty-six patients with a history of LSD use (average number of experiences was 88) with an average duration of 2 years since last use, were studied in an experiment of color discrimination. A control group of 31 patients, with unspecified criteria for matching, were also studied. The LSD users were further divided into those with flashbacks (see below) (25 per cent) and those without flashbacks. No difference was found between the two LSD groups, but the controls scored significantly better than the LSD groups. Once more, however, these findings must be interpreted with some skepticism, as other drug use and pre-drug use testing were not included.

There are surprisingly few case studies of the chronic, undifferentiated, ego-syntonic psychotic state, gradually resulting from hundreds of psychedelic drug experiences during difficult maturational periods in the patients' lives (59, 60). These individuals closely resemble chronic undifferentiated schizophrenics and are quite disabled and treatment resistant. They are often referred to as "burnt out." Very little is known about predisposing features, family history, motivations for use, etc., for these individuals.

In summary, it appears that nonpsychotic individuals who have taken LSD a large number of times appear to have particular personality characteristics that may or may not have predated their use of LSD (116). They may be described in terms of being somewhat odd, noncompetitive, and eccentric, but are not grossly impaired. The critical question that remains is whether these particular characteristics belong to a group of individuals who seek out, and are reaffirmed in their beliefs by, altered states of consciousness, including psychedelic-drug-induced ones, or if the experiences themselves are etiological. Evidence appears to point toward the former explanation.

The question of long term organic impairment has beem complicated by poorly controlled studies. However, the most carefully performed studies to date do not lend evidence to support the contention that frequent LSD use is associated with permanent brain damage.

Flashbacks. These are *intermittent* phenomena which may last for some time after psychedelic drug use (up to years) and are one of the most intriguing forms of "chronic" psychedelic drug-induced altered states of consciousness. They may be defined as transient, spontaneous recurrences of the psychedelic drug effect appearing *after a period of normalcy* following a psychedelic drug experience (168). Schick and Smith (140) have divided these into a) "perceptual," b) "somatic," and c) "emotional," depending upon the predominant aspects of the experience.

The reported incidence of flashbacks varies from 15 to 77 per cent (21, 79, 113, 140, 148, 163) in those subjects who have had at least one psychedelic experience. Subjects will often not report these phenomena, however, either because of their acceptance of flashbacks as part and parcel of the psychedelic drug subculture's expectations, and/or because of the general positive connotation these experiences have, *i.e.*, they are sometimes referred to as a "free trip." As was described in the preface to *Adverse Reactions*, using the term "adverse" when discussing flashbacks can also be fraught with interpretive difficulties.

The etiology of flashbacks is a topic of debate at the present time. Various theories have been proposed and may not necessarily be mutually exclusive, depending on the subject population.

Although predisposing factors in the development of flashbacks have not been as well documented as for

the more severe psychopathological reactions described above, it does appear that a greater number of psychedelic drug experiences in subjects may increase the likelihood of flashback development (*e.g.*, 124). There is some sense that perhaps those with adverse acute or chronic reactions may be more likely to develop and/or report such phenomena (79).

Matefy and co-workers (108, 109, 111, 112) have shown that "flashbackers" show no significant psychopathological differences as measured by the MMPI, or attentional processes as measured by the Embedded Figures Test, as compared to "non-flashbacking" drug users. Flashbackers have also been shown to score higher on a hypnotic suggestibility scale than nonflashbacking drug users. This research group flavors a "role-playing" model of flashbacks, whereby the phenomenon is described as a reaction learned during a state of high arousal resulting from drug use. Therefore, under other nonspecific high arousal states, a "psychedelic effect" is again experienced by means of conscious or unconscious association.

Other groups (72, 73, 124) believe that flashbacks are a result of situationally induced exacerbations of pervasive personality characteristics. These characteristics would lead toward the experiencing of flashbacks in circumstances that tend to induce altered states of awareness, *e.g.*, decreased sensory input, fatigue, fever (142), extreme relaxation (110), stress, marijuana use (49, 149), and emergence into a dark environment (4).

Psychodynamic formulations (81, 134) consider flashbacks to be comparable to conversion reactions/traumatic neuroses where defensive functions of the ego are incapable of completely repressing memories/conflicts that were stimulated/exacerbated by the intense psychedelic drug-induced effects. Symptomatic expressions (flashbacks) are the result.

Rosenthal (132), in one of the earliest reports of flashback phenomena, proposed a physiological, neurochemical basis of flashbacks, which has been elaborated upon by Abraham (4), who hypothesizes that LSD's effect on visual pathways routed through the lateral geniculate nucleus could result in "visual seizures."

LSD as a Model of Schizophrenia

One of the major differential diagnostic questions confronting the clinician in the case of psychedelic-related psychoses is that of schizophrenia. In the early years of psychedelic drug research, there was hope that a psychedelic drug-induced altered state of consciousness could provide a "model psychosis," whereby theoretical and clinical tools could be brought to bear on an easily inducible, reproducible, and reversible state resembling schizophrenia (27). Several excellent reviews of this subject have appeared, beginning with Hollister's in 1962 (78). Subsequent studies (71, 91, 96, 104, 171) using a variety of approaches have all confirmed that there are significant major differences between these two syndromes, especially in comparing psychedelic drug-induced states with the chronic form of schizophrenia. There appears to be a greater similarity between LSD-induced states and acute schizophrenia, but careful observation can still usually distinguish these two states.

Affectively, LSD states show less flattening of mood than schizophrenia. Visual perceptual alterations (hallucinations, illusions) generally predominate in LSD states compared to schizophrenia, where auditory perceptual changes hold sway. LSD-induced states tend to show less well fixed delusional symptoms than schizophrenia, most likely due to the acknowledgment of the drug-induced nature of their experience.

Historically, the knowledge that a patient has taken a psychedelic drug is of obvious value in clinical diagnosis. Also, the absence or presence of a family history of schizophrenia is helpful, as is premorbid history, in arriving at a quick working differential diagnosis, viz., the etiology of a particular psychotic episode.

Treatment and Course

Treatment of *acute panic reactions* should be directed toward allaying the patient's overwhelming anxiety. A quiet, comfortable room with a minimum of distractions should be available, and the patient should not be left alone. Most of these individuals can be "talked down" by calmly discussing their fears and fantasies, orienting the patient as necessary, reinforcing the concept that the experience is drug induced and time limited, and that no permanent brain damage has been suffered.

For more severe agitation, minor tranquilizers such as diazepam should be used, in oral or parenteral form (chlordiazepoxide is preferable for intramuscular use, as its absorption by this route is more consistent than for diazepam). Usual doses range from 15 to 30 mg for diazepam (50 to 100 mg for chlordiazepoxide) repeated every hour or two as necessary to calm or sedate the patient (154, 164).

Major tranquilizers should be reserved for only the most disturbed and agitated patients. Chlorpromazine was initially believed to be a specific LSD antagonist (5), but paradoxical reactions (138) and the problems of hypotensive and anticholinergic crises when used with 2,5-dimethoxy-4-methylamphetamine ("STP") and PCP (101, 143, 144) would point toward using

haloperidol (5 to 10 mg intramuscularly, or 10 to 20 mg by mouth), a high potency antipsychotic with minimal anticholinergic effects, every hour, as necessary. Antiparkinsonian drugs (*e.g*, benztropine or trihexphenidyl) should be available for use in the case of acute extrapyramidal side effects from haloperidol.

Restraint and/or gastric lavage are generally avoided in a frightened, hallucinating patient, although where there is a concern that the patient may hurt himself or herself, or others, or where other more potentially life-threatening drugs have been ingested, these procedures might be necessary.

Hospitalization is usually not necessary, but should be available. Once the acute reaction has subsided (usually within 12 to 24 hours), the patient should be sent home with someone responsible for monitoring him or her for the next 12 to 24 hours. A follow-up appointment should be arranged in order to evaluate the need for further therapy (68). The prognosis is generally good for uncomplicated panic reactions, and many drug users will curtail the use of these drugs subsequently on their own.

The treatment of the "LSD psychoses," as the previous discussion of these states would imply, will vary with the salient symptomatology (14). Tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, major tranquilizers, lithium carbonate (80), ECT (44, 53, 119), vitamin B_3 (75), and the serotonin precursor, L-5-hydroxytryptophan (2) have all been used, with varying rates of success. A period of drug-free observation for at least several days if possible, using only minor tranquilizers as necessary, and then treating the resulting clinical picture as it comes more clearly into focus, would seem the most prudent means of clinical management.

Treatment of flashbacks should be tempered by the fact that they are usually self-limited and diminish in duration, intensity, and frequency with time. The individual often responds to assurance and education about the phenomena, but if extremely panicky, the treatment should be similar to that of the acute panic reactions. Minor tranquilizers may be used acutely, and on a judicious, time-limited, "as needed" basis. Behavior modification (107), ECT (44), diphenylhydantoin (156), psychotherapy (134), and other pharmacotherapeutic strategies, including haloperidol (which may transiently increase visual flashbacks [118]) and benzodiazepines (4) have all been used, also with varying rates of success.

Patients should be advised that their flashbacks will most likely increase if psychedelic drugs are used again, as may also be the case with stimulants and/or marijuana. Persistently troublesome or increasing flashbacks indicate the need for a more thorough psychiatric and/or neurologic work-up. The prognosis for flashbacks, if the patient refrains from further use of mind-altering drugs, is generally good.

Summary and Conclusions

The mid-1950s to mid-1960s showed a great burst of enthusiasm for the therapeutic, growth-enhancing, and heuristic value of LSD-25 and other psychedelic drugs. However, the increasingly reported and occasionally lethal adverse reactions to these drugs in unsupervised settings made subsequent obtaining and using psychedelics in human subjects quite difficult. Their black market use, on the other hand, continued to flourish, and it is unfortunate that the only current data on the use of psychedelics are being generated by street-drug-using "LSD casualties" outside of major psychiatric research centers.

Adverse reactions to this class of psychoactive drugs can be conceptualized as occurring along a temporal continuum with acute panic reactions that often resolve spontaneously within a day, and chronic undifferentiated psychotic, treatment-resistant cases, at the two ends of the spectrum. In between exist "LSD psychoses," lasting longer than 1 to 2 days after the ingestion of a psychedelic compound, and "flashbacks," transient recurrences of some aspects of the original LSD experience after an intervening period of normality.

The research on adverse reactions to psychedelic drugs is fraught with methodological difficulties. Many of these have been addressed in this paper, and suggestions for data to be included in an "ideal" study have been given.

With the available data, it appears that the incidence of adverse reactions to psychedelic drugs is low, when individuals (both normal volunteers and patients) are carefully screened and prepared, supervised, and followed up, and given judicious doses of pharmaceutical quality drug. The few prospective studies noting adverse reactions have fairly consistently described characteristics predicting poor response to these drugs. The majority of studies of adverse reactions, retrospective in nature, have described a constellation of premorbid characteristics in individuals seeking treatment for these reactions where drugs of unknown purity were taken in unsupervised settings.

The relationship between drug-induced mental illness and mental illness *accompanied* by psychedelic drug use has been discussed. The majority of studies have focused primarily on "schizophrenia-like" illnesses and seem to indicate a fairly similar clinical picture and course for both schizophrenics who have or have not used psychedelic drugs. A possible rela-

tionship between affective disorders and LSD psychoses has been raised.

The "long term effects" of LSD use have been studied in a variety of settings and populations. Objective data in normal volunteers do not appear to tap the subjective sense of subjects' changed internal worlds, although individuals who appear to use LSD regularly as a tool for consciousness alteration have been found to show a characteristic personality and coping style. Long term psychiatric sequelae in patients have been studied in surprisingly few large case load reports, with a very tentative conclusion being that chronic, heavy LSD use appears to produce an unusually ego-syntonic disorder, in fringe-element type individuals, which is quite resistant to treatment.

Comprehensive and well controlled studies of neuropsychological function have generally failed to discern significant differences between groups of LSD users and controls.

Studies of flashbacks have also focused on the description of subject characteristics who experience these usually short-lived, delayed, intermittent phenomena, and have generally found an incidence of about 50 per cent. Populations experiencing these events have been found to be of varying degrees of psychopathology and associated drug use, thus engendering quite different causal explanations for their occurrence.

Etiologies of adverse reactions to psychedelic drugs have been proposed, from psychodynamic, behavioral, and biological perspectives. The systems approach to understanding these disorders has also been introduced.

Suggestions for Further Research

The human neurobiology of psychedelic drugs is still poorly understood. Several of the recently described biological markers for the major functional disorders, *e.g.*, platelet MAO activity in schizophrenia, and abnormal cortisol suppression in response to exogenous steroids in depression, might possibly be used to analyze more carefully the effect of psychedelic drugs on relevant biological parameters. Newly refined means of computer-assisted power band and spectral analyses of EEGs and evoked potentials, and the effects of psychedelics on these, may also provide additional insights into the mechanism of action and effect of these drugs. A particularly exciting development in neurobiological research is that of positron emission tomography (PET) scanning, whereby radioactively labeled pharmaceutical agents can be shown to bond to specific brain sites *in vivo*. Labeling psychedelic compounds in this manner could possibly help elucidate localization of their effects, as could studying the effect of LSD on regional metabolism of other compounds (*e.g.*, dopamine or serotonin).

From a clinical perspective, it appears that certain individuals should probably be excluded from psychedelic drug research participation in the future—these are those with either overt, or a history of, severe mental illness, unless they were institutionalized at the time of drug exposure and could be followed in a carefully supervised setting for at least 1 to 2 weeks after the drug experience, or after any acute sequelae resolved. Individuals with poor object relations (*e.g.*, unemployment, uninvolved with a significant other, or showing "downward drift") or those with primary defensive mechanisms including projection, denial, and tendency toward psychotic thought disorders, should also be included in drug studies only with the utmost caution and close follow-up. Individuals who are currently well functioning but have a family history of mental illness, especially schizophrenia, should be enlisted with extra caution, and perhaps screened with some of the more current biological markers to test for presence of "trait" abnormalities.

There are several psychological areas that call for expanded investigation. One is a further elucidation of the phenomenology of the psychedelic state, particularly with regard to some other, recently well studied altered states of consciousness, *e.g.*, the so-called near death experience, and states of religious exaltation. In my own observations of students of meditative disciplines in various settings, I have often struck upon a theme that runs through the motivation of many of these students; that is, psychedelic drugs led them to discover the existence of these "sublime" states, but were too unpredictable and toxic for regular use. Preparation for the development of the gradual unfolding of various states of consciousness was a much appreciated element of these individuals' involvement in meditative disciplines. Grof (65) has attempted to draw together these disparate phenomena in a cohesive framework. Much more work is needed, and a topographical map of consciousness could begin to be drawn up. Buddhist psychological works have recently been published (30) and have been shown to have heuristic value in describing various levels of altered states of consciousness (62, 150). Their relevance to the studies of psychedelic states remains uninvestigated, although Hofmann, the discoverer of LSD, has suggested that psychedelics' use be returned to that of a "sacred" drug, useful in supplementing meditational practices for the attainment of religious insights (77).

Another clinical use for psychedelics is in terms of therapeutic values. Who can benefit from psychedelic-assisted psychotherapy? How best to utilize these agents? What agents are most useful with what groups? For example, some early work seemed to

indicate a particularly positive therapeutic response to LSD in sociopaths (47, 136), a traditionally very treatment-resistant group. Intriguing are the reports of helping the dying with the aid of psychedelic drugs (66, 67).

The development of agents with specific characteristics, in terms of duration of action, side effects, with specific perceptual, cognitive, or emotional effects could be pursued, using carefully prepared and trained individuals (153) in order to match more carefully drug with specific therapeutic requirements.

With the severe restrictions placed on research with psychedelics in the 1960s, investigative work with psychedelic drugs has ground to a halt. It appears that, with proper restrictions and safeguards, it might be time to carefully begin this work again. The question of reinstituting psychedelic research in humans is bound to arouse powerful arguments both for and against. My feeling is that a decade of inactivity in this area of research has given us the necessary time to reflect on what has been learned and what needs further investigation. The relative roles of set and setting, motivations for drug use, personal and family history of mental illness, defensive style, and level of object relatedness, should all be used in careful selection, screening, and preparation of subjects for psychedelic research. It appears that, if these factors are carefully controlled, the incidence of acute and more long term problems associated with their use can be kept to a minimum. The benefits that can be obtained in terms of an increased knowledge of psychedelic drug-induced altered mental states, and their potential therapeutic roles, seems to justify these risks.

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