D-Lysergic Acid Diethylamide (LSD)

Investigator's Brochure

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Investigator's Brochure: Lysergic Acid Diethylamide

Drug Substance and Formulation

d-Lysergic acid diethylamide (LSD-25, LSD, lysergide) has the chemical formula of $C_{20}H_{25}N_3O$. It is an ergot derivative first synthesized by Albert Hofmann in 1938. Hofmann was the first to experience the subjective effects of LSD in 1943 (Hofmann 2005). Thereafter, Stoll conducted studies of LSD effects in humans (Stoll 1947; 1949). Other studies in Europe and North America followed (Nichols 2004). It is classified as a hallucinogen. More specifically, LSD, the tryptamine psilocybin and the phenethylamine mescaline all share at least one mechanism of action, that of being at least partial agonism at the serotonin $5HT_{2A}$ receptor. To date, there are no known natural sources of LSD, though morning glory and baby Hawaiian woodrose seeds contain lysergic acid amides (LSAs). LSD is chiral, and only d-LSD is active.

Pharmacological and toxicological effects

LSD Actions on Neurotransmitter Systems

Overview

LSD possesses a complex pharmacological profile that includes direct activation of serotonin, dopamine and norepinephrine receptors. In addition, one of its chief sites of action is that of compound-specific ("allosteric") alterations in secondary messengers associated with $5HT_{2A}$ and 5HT2C receptor activation and changes in gene expression. The hallucinogenic effects of LSD are likely due to agonism at $5HT_{2A}$ and $5HT_{2C}$ receptors (Aghajanian and Marek 1999; Nichols 2004), with at least one drug discrimination study in rats finding that a $5HT_{2A}$ receptor antagonist (ritanserin) was more successful than a $5HT_{2C}$ antagonist (SB 46349B) at eliminating LSD stimulus cues (Appel, West et al. 2004). However, LSD is also an agonist at the majority of known serotonin receptors, including $5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, 5HT5A, 5HT6 and 5HT7 receptors (Boess and Martin 1994; Eglen, Jasper *et al.* 1997; Hirst, Abrahamsen *et al.* 2003; Nichols and Sanders-Bush 2002). The only serotonin receptor for which LSD fails to show significant affinity is the 5HT3 receptor, the only serotonin receptor that is a ligand-gated ion channel rather than a G-protein coupled receptor. LSD also has affinity for dopamine D_1 and D_2 receptors (Creese et al. 1975; Nichols et al. 2002). Drug discrimination studies in rodents suggest that dopamine receptors may play a role in producing effects appearing after and in addition to changes associated with 5HT2A activation (Marona-Lewicka and Nichols 2007; Marona-Lewicka et al. 2005), and behavioral observations suggest that LSD may produce some effects through the dopamine system (Burt, Creese et al. 1976; Chiu and Mishra 1980; Watts, Lawler et al. 1995). There is some evidence that LSD has affinity for alpha adrenergic receptors (Marona-Lewicka and Nichols 1995; U'Prichard et al. 1977). Clonidine potentiated the LSD stimulus in rats trained to recognize LSD, an effect that suggests at least indirect action on these receptors (Marona-Lewicka and Nichols 1995). By contrast, LSD appears to have little to no affinity for histamine receptors (Green, Weinstein et al. 1978; Nichols,

Frescas et al. 2002), and the only evidence of action at acetylcholine sites is indirect. A more systematic presentation of LSD receptor affinity is provided in the table below (table adapted from and with permission from M Baggott). An *in vitro* study also suggests that LSD is an agonist at trace amine receptors (TAR) (Bunzow, Sonders et al. 2001). The functional significance of activity at trace amine receptors remains unclear, given that stimulants and entactogens (MDMA-like drugs) also activate these receptors (Bunzow, Sonders et al. 2001; Miller, Verrico et al. 2005).

LSD and Serotonin $5HT_{2A}$ and $5HT_{2C}$ receptors

Nearly all known 5HT2A agonists produce hallucinogenic effects in humans, and rodents generalize from one $5HT_{2A}$ agonist to another (Aghajanian and Marek 1999; Nichols and Sanders-Bush 2004). Phenethylamine hallucinogens such as mescaline and indoleamines, such as the ergoline LSD and the tryptamine psilocybin, all demonstrate $5HT_{2A}$ agonism. Despite it producing effects at the lowest doses, Nichols notes that LSD activity at $5HT_{2A}$ receptors is unremarkable. Hence it seems likely that the activity at other receptor sites may amplify the effects of LSD. One candidate may be the $5HT_{1A}$ receptor. More tryptamine hallucinogens act as $5HT_{1A}$ agonists than phenethylamine hallucinogens. Studies in nonhuman animals support the significance of $5HT_{2A}$ and $5HT_{1A}$ receptors in producing the hallucinogenic effects of LSD (Appel et al. 2004; Marona-Lewicka et al. 2005; Nichols and Sanders-Bush 2004; Winter and Rabin 1988). Humans still exhibited reduced visual attentional tracking after receiving psilocybin and a $5HT_{2A}$ antagonist, suggesting that other receptors, possibly such as $5HT_{1A}$ or $5HT_{2C}$, are responsible for these effects (Carter, Burr et al. 2005). The role played by $5HT_{1A}$ receptor in the stimulus characteristics of LSD in rodents is not entirely clear, since a $5HT_{1A}$ agonist only partially substitutes for LSD in rats trained to distinguish between LSD and saline (Cunningham and Appel 1987). It is also notable that *in vitro* studies found LSD to be a powerful $5HT_{2C}$ agonist (Burris et al. 1991; Sanders-Bush et al. 2003). However, while LSD had high affinity for $5HT_{2C}$ receptors, it also has low efficacy (Fiorella, Helsley et al. 1995; Fiorella, Rabin et al. 1995; Fiorella, Rabin et al. 1995), meaning that it does not maximally activate $5HT_{2C}$ receptors. As noted earlier, a $5HT_{2A}$ antagonist reduced LSD stimulus cues, while a $5HT_{2C}$ antagonist failed to attenuate these cues, and $5HT_{2C}$ antagonists did not prevent disruption of pre-pulse inhibition in rats (Ouagazzal et al. 2001). Some later-appearing effects of LSD may be the result of indirect or direct action at dopamine receptors (Creese, Burt et al. 1975; Marona-Lewicka, Thisted et al. 2005; Minuzzi, Nomikos et al. 2005). In humans, chronic tricyclic antidepressants amplified the subjective effects of LSD, and chronic use of selective serotonin reuptake inhibitors (SSRIs) attenuated LSD effects (Bonson et al. 1996; Bonson and Murphy 1996). SSRIs may upregulate or otherwise enhance responses on serotonin receptors that oppose the effects of $5HT_{2A}$ receptors (Aghajanian and Marek 1999).

Table 1: Affinity of LSD for Various Receptors

Receptor	Ki (nM)	Hot Ligand	Species	Source	Reference
5-HT_{1A}	1.1	^{3}H-8-OH-DPAT	Human	Cloned	(Nichols et al. 2002)
5-HT_{1B}	3.9	^{3}H-GR-125743	Rat	Cloned	Nichols et al. 2002
5-HT_{1D}	14	^{3}H-5-HT	Human	Cortex	Peroutka et al. 1989
5-HT_{1E}	93	^{3}H-5-HT	Rat	Cloned	Nichols et al. 2002
5-HT_{2A}	2.7	^{3}H-DOB	Human	Cloned	Egan et al. 2000
5-HT_{2B}	30	^{3}H-LSD	Rat	Cloned	Nichols et al. 2002
5-HT_{2C}	5.5	^{125}I-DOI	Rat	Cloned	Nichols et al. 2002
5-HT_{3}	33000	^{3}H-Quipazine	Rat	Cortex	Milburn and Peroutka 1989
5-HT_{4L}	1000	3H-GR-113808	Rat	Cloned	Gerald et al. 1995
5-HT_{5A}	9	^{3}H-LSD	Rat	Cloned	Nichols et al. 2002
5-HT_{5B}	3.23	^{3}H-5CT	Rat	Cloned	Boess and Martin 1994
5-HT_{6}	2.3	^{3}H-LSD	Human	Cloned	Hirst et al. 2003
5-HT_{7}	6.6	^{3}H-LSD	Rat	Cloned	Nichols et al. 2002
5-HT_{7L}	10	^{3}H-5-HT	Rat	Cloned	Eglen et al. 1997
Adrenergic Alpha	220	^{3}H-Clonidine	Rat	Brain	U'Prichard et al. 1977
Adrenergic Beta1	140	^{125}I-Pindolol	Rat	Cloned	Nichols et al. 2002
Adrenergic Beta2	740	^{125}I-Pindolol	Rat	Cloned	Nichols et al. 2002
Dopamine D_1	180	^{3}H-SCH23390	Rat	Cloned	Nichols et al. 2002
Dopamine D_2	120	^{3}H-NMSP	Rat	Cloned	Nichols et al. 2002
Dopamine D_3	27	^{3}H-NMSP	Rat	Cloned	Nichols et al. 2002
Dopamine D_4	56	^{3}H-NMSP	Rat	Cloned	Nichols et al. 2002
Dopamine D_5	340	^{3}H-SCH23390	Rat	Cloned	Nichols et al. 2002
Histamine H_1	1540	^{3}H-Pyrilamine	Rat	Brain	Nichols et al. 2002

Table adapted from Baggott, protocol for LSD pilot study, unpublished used with permission

Daily doses of LSD reduced numbers of $5HT_2$ receptors in rat brain without reducing any $5HT_1$ family receptors, alpha or beta adrenergic receptors, or dopamine D_2 receptors (Buckholtz et al. 1990), a feature it shared with the tryptamine hallucinogen psilocybin. Research examining compound-specific effects on secondary messenger systems found that both psilocybin and LSD stimulated arachidonic acid when activating rat $5HT_{2A}$ receptors, but that LSD stimulated the phosphoinositide (PI) pathway more strongly than psilocybin (Kurrasch-Orbaugh et al. 2003). However, the intrinsic activity of both serotonergic hallucinogens is similar. Since investigations of compound-specific or "allosteric" trafficking are new, the functional significance of this difference remains unclear.

LSD and $5HT_1$ Family Receptors

Evidence from *in vitro* and behavioral studies suggests that LSD acts upon $5HT_{1A}$ receptors. It has a high affinity for these receptors (Nichols, Frescas et al. 2002), and rats at least partially generalized from LSD to the $5HT_{1A}$ and $5HT_7$ agonist 8-OH-DPAT (Appel et al. 2004; Cunningham and Appel 1987; Reissig et al. 2005; Winter and Rabin 1988). The addition of several $5HT_{1A}$ agonists, including buspirone and 8-OH-DPAT, enhanced detection of LSD at doses lower than the training dose, while the $5HT_{1A}$ antagonist WAY100635 abolished this effect (Reissig et al. 2005). LSD acts on $5HT_{1B}$

receptors, though repeated administration does not reduce or increase receptor numbers (Nichols et al. 2002), and LSD also has a strong affinity for $5HT_{1D}$ receptors (Zgombick et al. 1996). Actions at these two receptors may be involved in the ability of LSD to abort cluster headaches (Sewell and Halpern In Press), but it is not clear whether either $5HT_{1B}$ or $5HT_{1D}$ receptor activity is involved in producing the subjective effects used in LSD-assisted psychotherapy.

LSD and Other Receptor Systems

LSD has a fairly high affinity to the recently discovered $5HT_{5A}$ receptor, found in both humans and rodents, and the $5HT_{5B}$ receptor, so far detected only in rodents (Grailhe et al. 2001). $5HT_{5A}$ knockout mice a blunted response to LSD, suggesting that these receptors may contribute to the behavioral effects of LSD (Grailhe et al. 1999). LSD is a partial agonist at $5HT_6$ receptors (Boess et al. 1997). In rat pre-pulse inhibition studies, administering $5HT_6$ antagonists failed to prevent LSD-associated attenuation in pre-pulse inhibition (Leng et al. 2003). However, it is notable that human pre-pulse inhibition studies using auditory startle often fail to match studies in rats, with drugs that attenuate PPI in rodents facilitating or having on effect on PPI in humans (e.g.Gouzoulis-Mayfrank et al. 1998a; Vollenweider et al. 1999). LSD binds to the $5HT_7$ receptor (Nichols et al. 2002). LSD served as a receptor antagonist in rat brain slices, while sumatriptan acted as an agonist (Hemedah, Coupar et al. 1999). Very little is known about the functional significance, if any, of LSD actions at these other receptors in humans, or the role played by $5HT_{5A}$, $5HT_6$, and $5HT_7$ receptors in generating the subjective effects of LSD. Though there is some indication that direct or indirect action at D_2 receptors may be involved in some effects of LSD, and one study suggests the possible involvement of D_4 receptors in at least later temporal effects of LSD (Marona-Lewicka and Nichols 2007), little is known about the direct or indirect effects of LSD on D_4 or D_5 receptors. LSD may affect other transmitter systems as well, such as adrenergic receptors (Marona-Lewicka and Nichols 1995; U'Prichard, Greenberg *et al.* 1977). It does not appear that LSD has significant interactions with the histmaminergic system (Nichols et al. 2002), though one study reports that LSD and a brominated relative Br-LSD are antagonists at H_2 receptors, while the non-psychoactive enantiomer l-LSD, mescaline and psilocybin were inactive at these receptors (Green et al. 1978). There is only tenuous evidence for any direct effects of LSD on the cholinergic system (Chiu and Mishra 1980), with the muscarinic antagonists atropine and scopolamine intensifying LSD-induced catalepsy in rats (Chiu and Mishra 1980). Early investigations of LSD effects in humans found that administering the adrenergic blocker phenoxybenzamine or the muscarinic cholinergic antagonist scopolamine failed to alter LSD effects (Isbell et al. 1959).

Possible interactions between LSD and neuropeptide systems remain a relatively unexplored area of research. Larson and colleagues reported that intrathecal (subarachnoid space) injections of 25 mcg/kg LSD prevented desensitization to repeated injections of substance P, so that pain-response behavior remained the same, but mice given Freund's adjuvant first and then LSD showed enhanced desensitization to substance P (Larson et al. 1989). It is not clear whether these changes are relevant to human LSD studies, given high doses and central route of administration.

LSD and Gene Expression

Researchers have examined the effects of LSD on gene expression in rat prefrontal cortex (Nichols and Sanders-Bush 2002) and in mouse somatosensory cortex (Gonzalez-Maeso et al. 2003). The large dose of 1 mg/kg i.p. produced changes in gene expression for a number of genes in rat brain (Nichols and Sanders-Bush 2002) including *c-fos*, *arc*, *serum glucocorticoid kinase* (*sgk*), *neuron-derived orphan receptor 1* (*nor1)*, *IKappaBeta* and k*rox-20*. LSD produces an early increase in *c-fos* and arc (Gresch et al. 2002), a protein found in dendrites and associated with cytoskeletal rearrangements, in prefrontal cortex (Lyford, Yamagata et al. 1995). *Krox-20* may be involved in the maintenance of long-term potentiation (Inokuchi et al. 1996), and *Nor1* is a protein for a nuclear steroid/thyroid receptor that may be involved in response to opiate and cocaine administration (Maruyama et al. 1995).

Gonzalez-Maeso and colleagues measured gene expression in mouse somatosensory cortex from wild-type and $5HT_{2A}$ knockout (KO) mice after administration LSD and other known $5HT_{2A}$ agonists and dopamine agonists, finding that LSD increased expression of the genes *egr1*, *egr2* and *period1* in wild-type mice (Gonzalez-Maeso et al. 2003). Knockout mice only had an increase in *IKBetaAlpha* gene expression. Currently, the significance of changes in gene expression is unknown. However, *period1* affects circadian rhythm and is one of five genes crucially involved in maintaining cellular rhythms (Cermakian, Monaco et al. 2001), and *egr1* activation is associated with long-term potentiation in the hippocampus (Wei, Xu et al. 2000). These gene products may play a role in changes in cognition relevant to subjective effects, and some researchers postulate that they are involved in the ability of LSD to interrupt cluster headache periods, described in more detail below (Sewell and Halpern In Press).

Psychological (Subjective) and Physiological Effects

Several hundred studies in various animal species have indicated the low toxicity of LSD. LD_{50} values for LSD are 50-60 mg/kg iv for mice, 16.5 mg/kg for rats, and 0.3 mg/kg for rabbits (Clark 1987; Haddad 1976; Rothlin 1957). On the basis of a single case series of near-fatalities, estimated lethal dose in humans may be 0.2 mg/kg or about 14,000 mcg (Klock et al. 1975). By comparison, previous human research generally employed doses between 25 and 500 mcg.

LSD Effects in Nonhuman Animals

LSD temporarily raised blood pressure in spinal cats and increased respiration in rabbits (Graham and Khalidi 1954b). LSD produces several distinctive behaviors in rodents, including head twitches in mice (Corne and Pickering 1967), "wet dog shakes" involving the whole body in the rat (Bedard and Pycock 1977), and reduction in locomotor and exploratory activity (Krebs-Thomson and Geyer 1996; Wing et al. 1990). These behaviors are not readily comparable to human responses to LSD. It is difficult to confirm the presence of perceptual alterations in nonhuman animals, but rhesus monkeys given known hallucinogens, including psilocybin and mescaline, reached out for invisible

objects, suggesting that the animals experienced perceptual alterations (Fantegrossi, Woods et al. 2004)

For a time researchers considered LSD to be a prototypical "$5HT_2$ agonist," and conducted *in vitro* and nonhuman animal studies using LSD in this role. However, as they learned that LSD acted on a wide array of serotonergic and non-serotonergic receptors, and when they faced the regulatory difficulties involved in doing research with a scheduled drug, the phenethylamine DOI supplanted LSD as a pharmacological probe in studies of $5HT_{2A}$ receptors. Consequently, very little research into the effects of LSD in vitro or in vivo has appeared in the last five to ten years.

LSD Effects in Humans

Physiological Effects

Physiological effects include slight increases in blood pressure and heart rate, vasoconstriction, pupillary dilation, increases in core body temperature, blood glucose levels, sweat and saliva production, and other signs of sympathetic system stimulation (Cohen 1967; Hollister 1968; Hollister and Hartman 1962; Isbell 1959) LSD did not consistently produce any of these physiological effects except pupillary dilation, and none of the physiological changes were clinically significant. For example, systolic and diastolic blood pressure increased by 14 and 8 mm Hg, respectively, and heart rate increased by 10 bpm after oral administration of 0.1 mg (100 mcg) LSD in ten men and two women (Graham and Khalidi 1954a), with cardiovascular effects peaking two to three hours post-administration and lasting for several hours. Dimascio and colleagues reported similar effects that peaked 2.5 hours and declined or began declining five to seven hours after administration of 1 mcg/kg (approximately 70 mcg) LSD administered to six men (Dimascio et al. 1957), including moderate increases in systolic and diastolic blood pressure.

There appear to be very few investigations of the neuroendocrine effects of LSD in humans, perhaps because interest in and capacity to assess these hormones arose after human LSD research had ceased, though there are a few studies in rats finding that LSD reduced serum prolactin (Meltzer, Fessler *et al.* 1977; Quadri and Meites 1971). Though there are elevated levels of peripheral $5HT_{2A}$ receptors in premenopausal women (Wihlback et al. 2004), to date there is no research indicating menstrual variation in LSD effects.

Psychological and Subjective Effects

Onset of LSD effects in humans begins 30 to 90 minutes after administration, with subjective and physiological effects generally lasting five to ten hours after drug administration (Abramson et al. 1955; Dimascio et al. 1957; Katz et al. 1968; Linton and Hain 1967; Nichols 2004) (Abramson et al. 1955; Dimascio et al. 1957; Linton and Langs 1962; Katz et al. 1968; Nichols 2004). Acute subjective effects may peak within the first two to four hours after LSD administration (Dimascio et al. 1957), with effects

waning seven to nine hours after administration (Linton and Langs 1962). The acute subjective and psychological effects of LSD are unpredictable and can vary widely across individuals, and within the same individual assessed at different times or in different surroundings (or settings) (Nichols 2004). Despite this wide variation, some of the subjective effects of LSD occur in most individuals and in most settings (Halpern and Pope 2003; Nichols 2004). These effects include labile mood, (rapid and sometimes extreme changes in mood), visual distortions and illusions, alteration in perception of time (as time speeding up or slowing down), depersonalization (feeling that the self is not real) and an altered sense of reality or derealization (feeling that one's surroundings are not real or that one is "in a dream") (Abramson, Jarvik et al. 1955; Nichols 2004). In most cases, people retain insight concerning perceptual illusions or distortions produced by LSD, and do not believe these experiences to be actual representations of the world around them. However, people may have unusual thoughts or feelings about themselves or the world. Higher doses of LSD and similar drugs, such as psilocybin, may not simply produce more intense effects than lower doses, but may produce an experience of an "alternate reality" or a transcendent experience (Nichols 2004; Pahnke, Kurland *et al.* 1971). Other common subjective effects include perceived unsteadiness, weakness, dizziness, and other odd or uncomfortable bodily sensations, referred to as somatization (Abramson et al. 1955) LSD effects are comparable to the tryptamine psilocybin and the phenethylamine mescaline (Hebbard and Fischer 1966; Hollister and Hartman 1962; Hollister and Sjoberg 1964; Isbell, Wolbach *et al.* 1961) including increased anxiety, peculiar thoughts, perceptual alterations, unusual body sensations, dizziness, and impaired concentration. Explanations for the perceptual, emotional and cognitive alterations produced by LSD and other $5HT_{2A}$ agonist drugs hypothesizes that effects are produced through disruption of brain "gating mechanisms (Vollenweider and Geyer 2001).

Low to moderate doses of LSD prolonged length of the first and second periods of rapid eye movement (REM) sleep (Muzio et al. 1966), and produced short bursts of REM-like activity during other stages of sleep. Higher doses produced a greater number of awakenings. Little else is known about the effects of LSD on sleep architecture.

Possibly as a result of changes in attentional focus and emotional lability, previous research suggests that LSD interferes with tasks requiring memory and attention while improving tasks involving creativity. Psychedelic doses of LSD acutely impaired performance on working memory tasks such as Digit Span and word recall (Jarvik et al. 1955), while having notable but small effects on measures of psychomotor speed or figure reconstruction (Barendregt 1960). LSD increased creative or unusual responses to word association tasks (Zegans et al. 1967), though responses varied with dose and with pre-existing individual differences. It is notable that more recent investigations reported that people given the tryptamine hallucinogen psilocybin also generated more unusual semantic associations (Gouzoulis-Mayfrank et al. 1998b; Spitzer et al. 1996).

Factors Influencing Psychological and Subjective Reactions to LSD

The variable effects of LSD are at least in part due to their sensitivity to the prior emotional or internal state of the individual or "set" and the state of the environment or surrounding, or "setting" (Grof 2000: 1980; Nichols 2004). Though to date there is no systematic or empirical investigation into the effects of set and setting, at least one previous study noted that people who reported better ability to handle stressful situations were also better able to perform attention and memory tasks under LSD (Jarvik et al. 1955). Psychiatrists and psychotherapists conducting psychotherapy often ensure that the setting where the therapy will occur features comfortable furniture and does not require contact with people outside of the therapy setting, and they often require that participants remain within the setting throughout the LSD-assisted therapy session. Using eyeshades in a therapeutic context is intended to lead to introspection rather than focus on external features of the setting and to intensify alterations in consciousness (Grof 2000: 1980).

Table 4:
QUESTIONS DISCRIMINATING BETWEEN ZERO AND FIFTY MICROGRAMS LSD
(N=11)

Questions	Percent responding positively in any hour		
	Zero LSD	50 μg LSD	t
	.01 level		
	none	none	none
	.02 level		
Do you feel unsteady?	9	91	3
Do you feel as if in a dream?	18	91	2.83
	.05-.03 levels		
Do you have funny feelings on your skin?	9	73	2.65
Do you tremble inside?	27	91	2.65
Is there pressure in your ears?	9	64	2.46
Do you have difficulty in focusing your vision?	0	55	2.46
Do you feel weak?	18	73	2.46
Do your hands and feet feel light?	9	55	2.24
	.10-.06 levels		
Are your lips drawn back as if you were smiling?	0	36	2
Do you feel dizzy?	36	73	2
Do you feel drowsy?	46	82	2
Is your skin sensitive?	9	55	1.89
Do your hands and feet feel peculiar?	27	73	1.89
	Approx. .10 level		
Is salivation increased?	18	46	1.74
Is your appetite increased?	27	55	1.74
Are you sweating?	18	46	1.74
Are you cold?	9	36	1.74
Do you feel fatigued?	55	82	1.74

From Abramson et al. 1955

Table from Baggott, protocol for LSD pilot study, unpublished

Table 5:
QUESTIONS DISCRIMINATING BETWEEN ZERO AND ONE HUNDRED MICROGRAMS LSD
(N=7)

Questions	Percent responding positively in any hour: Zero LSD	100 μg LSD	t
	.02-.01 levels		
	none	none	none
	.05 level		
Are things moving around you?	0	86	2.46
Do you feel unsteady?	14	100	2.46
Do you have funny feelings on your skin?	0	86	2.46
Do you feel weak?	14	100	2.46
Do you feel as if in a dream?	14	100	2.46
	.10-.06 levels		
Do you feel ill in any way?	14	86	2.27
Are you nauseated?	0	71	2.27
Do you feel dizzy?	29	100	2.27
Is your skin sensitive?	0	71	2.27
Do your hands and feet feel peculiar?	14	86	2.27
Do you tremble inside?	29	100	2.27
Are you sweating?	14	71	2
Do your hands and feet feel light?	0	57	2
Is your eyesight blurred?	14	71	2
Do you have difficulty in focusing your vision?	0	57	2
Do things seem too far away?	0	57	2
	Approx. .10 level		
Have you a feeling of choking?	0	43	1.73
Are your lips numb?	0	43	1.73
Is there difficulty in breathing?	0	43	1.75
Are you cold?	0	43	1.73
Is there pressure in your ears?	0	43	1.73
Are shapes and colors altered in any way?	0	43	1.73

From Abramson et al. 1955

Table from Baggott, protocol for LSD pilot study, unpublished

Pharmacokinetics and biological disposition

LSD is metabolized in the liver. *In vitro* studies with human liver microsomes suggest that LSD is chiefly metabolized through de-ethylation by one of the P450 CYP enzymes and by enzymes that are currently unidentified (Aghajanian and Bing 1964; Wagner et al. 1968). LSD is first detectable in plasma in humans 15 to 30 minutes after oral administration, and it has an elimination half-life of 175 minutes, or almost three hours, with plasma levels of LSD steadily declining over an eight hour period (Wagner et al. 1968). However, a more recent study found LSD half-life to be 5.1 hours, with a peak concentration of 1.9 ng/mL (Papac and Foltz 1990). Major metabolites may include lysergic acid ethylamide, 2-oxo-3-

hydroxy-LSD, some mono-oxylated and trioxylated LSD, lysergic acid ethyl-2-hydroxyethylamide and 13 and 14-hydroxy-LSD, and their glucuronide conjugates in urine (Cai and Henion 1996; Canezin et al. 2001; Poch et al. 1999). Comparing the findings of Papac and Foltz with findings from a study using LSD injection (Aghajanian and Bing 1964) indicates that LSD is well absorbed with a bioavailability that may be around 70%.

Several groups have characterized urinary metabolites. The main urinary metabolite in biosamples from two illicit LSD users was 2-oxo-3-hydroxy-LS in a study of biosamples from two illicit LSD users (Canezin et al. 2001). This metabolite may be as much as 16 to 43 times higher than LSD in blood and urine specimens (Cai and Henion 1996; Canezin et al. 2001; Poch et al. 1999; Reuschel et al. 1999). Nor-LSD, Nor-iso-LSD, lysergic acid ethylamide, trioxylated-LSD, lysergic acid ethyl-2-hydroxyethylamide and 13 and 14-hydroxy-LSD and their glucuronide conjugates have also been detected in urine. Klette and colleagues (Klette et al. 2000) studied the formation of 2-oxo-3-hydroxy-LSD and 2,3-dihydroxy-LSD in human liver microsomes and preserved hepatocytes, finding that both metabolites formed in a time-dependent manner that could be prevented with the nonspecific cytochrome P-450 inactivator 1-aminobenzotrizole. Klette et al. suggest three possible metabolic pathways, summarized in Figure 1.

LSD distribution has been studied in the mouse and rat (Boyd 1956; Haley and Rutschmann 1957; Siddik et al. 1979; Stoll et al. 1955) guinea pig (Siddik et al. 1979), cat (Siddik et al. 1979) and rhesus monkey (Boyd 1956). Distribution figures from two of these studies are presented in Tables 2 and 3 below.

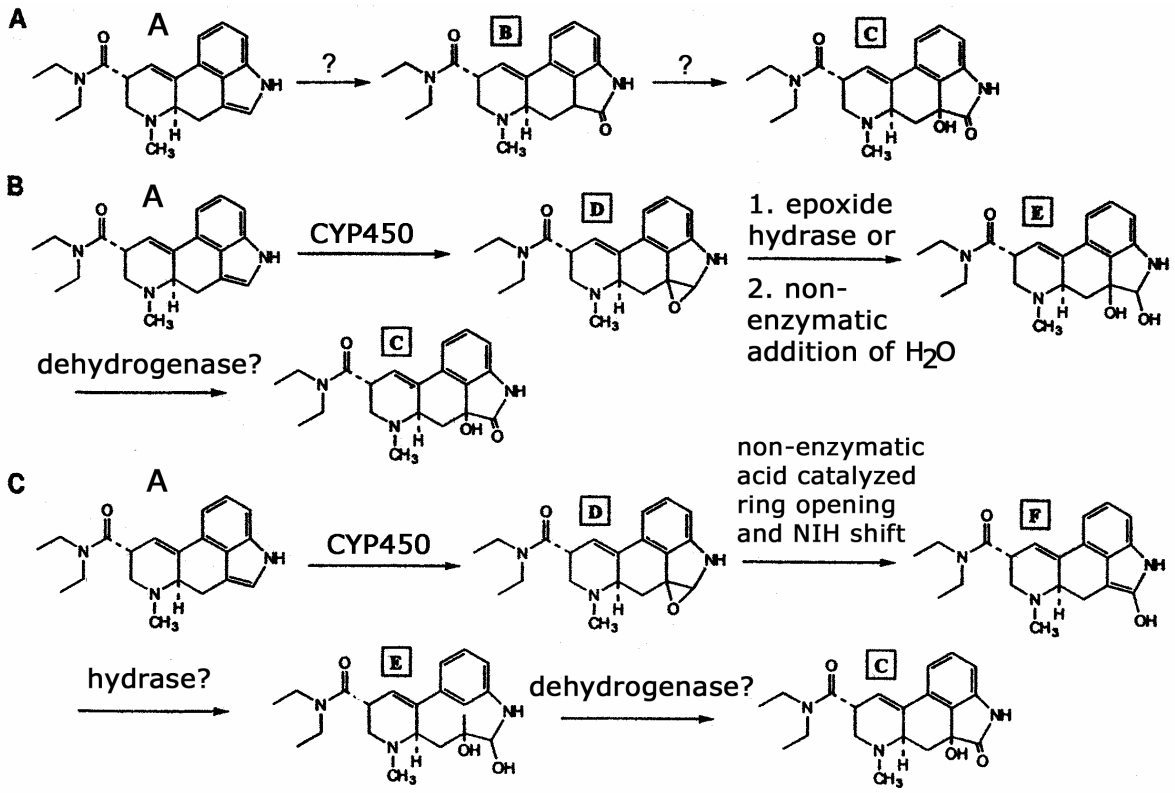

Figure 2. LSD metabolic pathways: A, via 2-oxo LSD intermediate; B, via epoxide intermediate and epoxide hydrase/nonenzymatic addition of water, unknown dehydrogenase activity; c, via epoxide intermediate, N.I.H. shift, Cyt P450, and unknown dehydrogenase activity. [A] LSD, [B] 2-oxo LSD, [C] 2-oxo-3-hydroxy-LSD, [D] LSD 2,3 epoxide, [E] 2,3-dihydroxy LSD, [F] 2-hydroxy LSD. From Klette et al. 2000, figure courtesy of M Baggott, for protocol for LSD pilot study, unpublished

Table 2: Tissue Distribution of LSD in the Rat*

	%	mg/mg (wet) x 10^{-6}
Gut Contents	70.2	…..
Liver	2.31	3.89
Spleen	0.08	1.33
Brain	0.02	0.21
Heart	0.03	0.55
Lung	0.12	1.13
Skeletal Muscle	0.09	0.4
Kidney	0.44	3.28
Uterus and Ovaries	0.06	0.74
Adipose Tissue	0.04	0.24
Gut (less contents)	10.2	17.8
Blood	…..	0.46
Rest of Carcass	7.55	0.53

*Measures were made three hours after administration of 1 mg/kg of labeled LSD intraperitoneally (from Boyd 1956)

Table 3: Tissue Distribution of LSD in the Cat*

Tissue	LSD
	mg/kg
Plasma	1.75
Cerebrospinal fluid	0.36
Brain	0.52
Liver	0.67
Kidney	0.53
Muscle	0.2
Heart	0.3
Lung	0.87
Spleen	0.38
Intestine	0.39
Fat	0.2
Bile	1.85

*Measures were made 90 minutes after the intravenous administration of 1 mg/kg, of LSD (from Axelrod et al. 1957)

Tables courtesy of Baggott, protocol for LSD pilot study, unpublished

Safety and effectiveness in humans

History of Research

There is a large literature on LSD in therapeutic (Grinspoon and Bakalar 1979; Mangini 1998) and research (Nichols 2004) contexts. Thousands of individuals received LSD in the context of psychiatric and psychological research or during psychotherapy in the 1950s and 1960s (Grinspoon and Bakalar 1981; Nichols 2004; Pahnke, Kurland *et al.* 1970; Strassman 1995). At the time, some researchers believed that LSD and other hallucinogens produced a "model psychosis" that would allow them to experimentally reproduce and study this mental disorder (Nichols 2004). However, even early publications expressed awareness that the alterations in consciousness produced by LSD were not equivalent to those seen with psychosis as defined in the mid-20th Century. Researchers investigated the perceptual and cognitive effects of LSD, including the effects of LSD on affect, cognition, creativity and sleep (Goldberger 1966; Jarvik et al. 1955; Muzio et al. 1966; Savage 1952; Zegans et al. 1967). Other researchers employed LSD as a psychotherapeutic adjunct in the treatment of anxiety, depression, "neurotic disorders" alcoholism, and in terminal illness (Denson and Sydiaha 1970; Grof et al. 1973a; Jensen 1962; 1963; Kurland et al. 1971; Kurland 1973; Ling and Buckman 1963; Martin 1957; Pahnke et al. 1970; Savage and McCabe 1973). In Switzerland, 170 patients with a wide array of clinical conditions received LSD between 1988 and 1993, and the results of this treatment were summarized in a case series (Gasser 1996).

No new human LSD studies have been published in the last two decades. However, a large number of previous human trials indicate that LSD can be safely administered within a research or psychotherapeutic setting. There is currently no ongoing human LSD research taking place in the US. The sponsor plans to support a study examining the safety and efficacy of LSD-assisted psychotherapy in people with anxiety arising from being in the advanced stages of a potentially fatal illness. Another sponsor intend to conduct a study examining the safety and efficacy of LSD as a means of interrupting chronic cluster headache.There are also plans to conduct a study of the acute effects of LSD on attention and cognition.

LSD in Psychotherapy and in Advanced Stage Illness

LSD in combination with psychotherapy reduced depression, anxiety and social isolation in alcoholics (Kurland et al. 1971). Some psychotherapists used LSD in combination with psychotherapy in people with advanced stage cancer (Grof et al. 1973b; Kurland 1973; Pahnke et al. 1969), a treatment that seemed to reduce anxiety and improve quality of life. Psychotherapists and psychotherapy researchers either used repeated low doses, or relied on larger single doses in the context of psychotherapy. At least two-thirds of people with advanced stage cancer who were enrolled in psychotherapy using doses of 200 mcg or more exhibited improved quality of life. For example, 36% of 40 people with advanced stage cancer given 200 to 500 mcg LSD in a psychotherapeutic context reported moderate improvement in overall emotional distress, and 36% reported dramatic improvement (Kurland 1973). Kast and colleagues found that people with cancer given LSD sometimes reported analgesia that outlasted the subjective effects of the drug (Kast 1966; Kast and Collins 1964). These early studies reported successful treatment outcomes with LSD-assisted psychotherapy (Nichols 2004; Strassman 1995). However, the psychiatrist and psychotherapists performing early LSD psychotherapy research did not conduct or document these studies with the rigor expected of current psychiatric research, so that many questioned the findings of efficacy (Nichols 2004).

LSD as Potential Treatment for Cluster Headache

Sewell and colleagues recently described the effects of LSD and the related tryptamine $5HT_{2A}$ agonist psilocybin on cluster headache, a form of headache associated with excruciating pain that can recur more than once a day and for periods of weeks or months (Sewell et al. 2006). They reported that seven of eight people found that LSD reduced or eliminated headaches occurring within their expected cluster headache period. Twenty-five of 48 people reporting psilocybin use during a cluster headache reported complete interruption of their cluster period, and 18 reported partial reduction. Though to date there are no controlled studies into the effects of LSD and other $5HT_{2A}$ agonists on cluster headache, the case series suggests that LSD may be efficacious in interrupting cluster periods and that hallucinogenic doses are not needed to produce this effect.

Possible risks and side effects

Overview and History

LSD is not associated with disease or damage to any organ or system (Nichols 2004). LSD in cats given 1 mg/kg was distributed to plasma, liver and brain (Axelrod et al. 1957, see also Table 2 above). A recent search conducted on the PubMed database in September, 2005 using the words "LSD" or "lysergic acid diethylamide" and various organs or medical terms ("heart," "cardiac," "liver") and "adverse event", and an additional search conducted in August 2006 with the words "lysergic acid diethylamide" uncovered only one case report of a mesenteric mass in a chronic LSD user (Berk et al. 1999), and failed to find any case reports of serious adverse effects or adverse effects on the heart, liver or kidney. Given that people have used LSD in research and non-medically for forty to fifty years, the lack of case reports of nonpsychiatric adverse events is notable. All serious adverse effects of LSD are psychological and are described below. Risk of acute or long term physiological adverse effects after administering sub-hallucinogenic or typical doses of LSD is apparently minimal.

Fatalities

To date, there have been only two fatalities deemed directly due to LSD (Fysh et al. 1985; Griggs and Ward 1977). However, the role played by LSD in both cases is questionable and information in these reports is poorly or incompletely reported. In one case, the dose taken was probably extremely high and the body was discovered one month after LSD ingestion, so the circumstances surrounding death are uncertain (Griggs and Ward 1977), and in the other case, the cause of death is unstated and the author failed to provide the medical history of the patient or the proximal cause of death (Fysh et al. 1985). Since both cases are poorly and incompletely reported, they leave serious questions about the presence, strength and nature of the tie between LSD and subsequent death.

Common Adverse and Side Effects

Common side effects of LSD are described above in "Physiological and Psychological Effects" and include sometimes intense and rapid changes in mood and perception, including intense positive and negative mood, unusual thoughts, perceptual illusions or distortions, including altered time perception, dizziness, derealization and depersonalization, and perceived unsteadiness or weakness. The most common acute adverse effects of LSD are all psychological, and include anxiety or panic response, a prolonged unpleasant experience (or "bad trip") and psychotic reactions. Common side effects and adverse effects of LSD are dose-dependent (Abramson et al. 1955) and transient, lasting no longer than the expected eight to 10 hour duration of drug effects.

Reckless Behavior

People who have taken LSD in uncontrolled settings may engage in reckless behavior, such as driving while intoxicated. The risk of reckless behavior occurring during controlled studies can be prevented or greatly reduced through continued supervision by the researchers and by keeping participants within the confines of the clinic or laboratory where the study is taking place for the duration of drug acute effects.

Anxiety and Panic Reactions

As reported in several reviews, transient anxiety or depression after taking LSD has been reported in many cases (Grinspoon and Bakalar 1979; Grof 2000: 1980; Strassman 1984). These cases typically resolve spontaneously with supportive care, but in some cases, treatment included administration of anti-psychotic or sedative drugs as well. In most cases, emergency room admissions arising from anxiety or psychological distress after LSD do not require continued hospitalization (Halpern and Pope 1999; Nichols 2004; Strassman 1984). A case series not evaluated by Nichols (2004) described a similar profile of acute adverse effects in people reporting illicit LSD use and reached similar conclusions (Blaho et al. 1997). Both acute and prolonged anxiety or psychotic reactions to LSD appear to be dose-dependent (Cohen 1960), with greater distress occurring with higher doses. The occurrence and intensity of anxiety or panic responses can be reduced through providing participants with information on potential drug effects prior to drug administration, supervision and monitoring the duration of drug effects by people trained to deal with panic or anxiety reactions, including those arising from hallucinogens, and use of ascending doses.

Transient and Prolonged Psychotic Reactions

Some individuals enter transient and sometimes prolonged psychotic states after LSD use (Cohen 1960; Halpern and Pope 1999; Strassman 1984). Researchers who reviewed case series and reviews of the relationship between LSD use and subsequent occurrence of psychosis note that often the evaluation of psychosis is made after LSD use only, and not prior to use (Strassman 1984), making it difficult to determine the degree of change after LSD use. After examining the literature, Strassman concluded that LSD might trigger psychotic episodes in people already vulnerable to psychosis rather than causing this reaction directly. Research that examined the prevalence of psychiatric reactions in response to LSD by ending surveys to investigators who had conducted studies with LSD or mescaline found that 0.08% of 5000 volunteers exhibited or reported having psychotic or extreme panic reactions that lasted more than two days (Cohen 1960). Cohen reported that the rate of occurrence of psychiatric symptoms reached the slightly higher rate of 0.18% among individuals who were psychiatric patients. An examination of hospital admissions from 1967 to 1971 collected in Canada found that only a small percentage (67 of 22,885) mentioned LSD, and many of these cases involve the use of multiple substances (1973). Another survey of 4300 research volunteers who had taken part in LSD research reported a rate of 0.9% for serious, persistent psychiatric reactions (Malleson 1971). These findings, in combination with more recent case series described

above, indicate that while LSD can provoke psychosis or other psychiatric symptoms in a very small percentage of people, it does not do so often, and that receiving a hallucinogenic drug as part of a research study is extremely unlikely to trigger persistent, or even transient, psychosis. Early research with LSD-related compounds did not apply as stringent criteria for participant selection or screening as would be used now, so the low rate of psychosis from these early studies is liable to overestimate the rate of prolonged psychological responses that might occur in a study that screens for past or present psychotic disorders. The occurrence of transient or persistent psychosis can be prevented or further reduced by screening subjects on the basis of past and current mental health and excluding people on the basis of the presence of past or current psychotic disorders or such disorders in first-degree relatives, such as biological parent or sibling.

Post-Hallucinogen Perception Disorder (HPPD)

Some people who have used serotonergic hallucinogens, such as LSD or psilocybin, experience persistent and distressing alterations in perception, chiefly in the visual system, that last from weeks to years after use. This condition is now diagnosed as hallucinogen persistent perception disorder (HPPD), and is no longer referred to by the term "flashbacks," which better describe an experience more akin to traumatic recall of an intensely upsetting experience, as a "bad trip." To date, there are no reports that assess the prevalence of HPPD in the general population, but an examination of previous reports and estimates of use of LSD and other hallucinogens use in the US suggests that HPPD is very rare (Halpern and Pope 2003). Halpern and Pope note that many to most previous studies were affected by selection bias. These reports also contained information supporting alternative explanations of flashbacks or HPPD, such as use of other drugs or the presence of other mental disorders, and found that people who had not used hallucinogens sometimes also reported experiencing similar perceptual disturbances. Preliminary data collected from 1000 hallucinogen users by Baggott (Baggott 2006) suggests that no more than 1% experienced HPPD. The risk of HPPD occurring after LSD administration can be reduced by screening participants for potential risk factors such as substance dependence and through excluding people reporting HPPD after prior use of hallucinogens.

Long-Term Personality Changes

Earlier studies found changes in personality or neuropsychological function after frequent chronic LSD use. A review of these studies concluded that all of these early studies shared a number of methodological flaws (Halpern and Pope 1999) that included retrospective study design and failure to account for effects that might arise from use of other drugs. In their review and analysis, Halpern and Pope concluded that long-term changes in personality or psychological function, if they existed at all, were liable to be subtle or not clinically significant. It is notable that when investigators contacted participants and their friends or relatives two months after administration of psilocybin in a randomized, active-placebo-controlled study, they found that participants and people who knew the participants well reported positive changes in their attitudes and behavior

(Griffiths et al. 2006). Monitoring personality before and after psilocybin administration will allow researchers to detect personality changes.

Abuse Liability

Currently, LSD is placed in US Schedule 1, defined as having no medical use and having high abuse liability, and is treated internationally as a controlled substance. Despite this designation, examining use patterns in humans and self-administration and conditioned aversion in rodents and nonhuman primates suggests that LSD possesses little or no abuse liability (Nichols 2004). Only one study found that LSD produced conditioned place preference, an indicator of reward value, in rats, but only in males of a specific rat strain (Meehan and Schechter 1998; Parker 1996). Most drugs with similar pharmacological profiles, such as psilocybin, also fail to produce consistent self-administration in rodents or monkeys (Fantegrossi, Woods *et al.* 2004; Nichols 2004). Rhesus monkeys found LSD to be aversive, working to avoid a cue associated with LSD infusion (Hoffmeister 1975). There is no human LSD dependence syndrome, and prevalence of LSD use in adolescents and young adults seems to remain relatively stable over time in the US (Johnston et al. 2004), as well as in Europe (see for example Soellner 2005). Hence it appears that LSD has little to no abuse liability, and participants receiving LSD are highly unlikely to develop dependence on it after exposure.

Reproductive Toxicity

Reports of chromosomal damage from exposure to LSD first described in *in vitro* studies conducted in the 1960s and 1970s (Cohen et al. 1967; Dishotsky et al. 1971) were later disputed by further research (Cohen et al. 1967; Dishotsky et al. 1971; Grinspoon and Bakalar 1979; Grof 2000: 1980). A review of 4815 former participants in trials with LSD found that 170 infants of participants, or 0.03%, had two commonly occurring birth defects, syndactyly or congenital dislocation of the hip (Grinspoon and Bakalar 1979). Examination of 148 pregnancies in illicit LSD users and matched controls also failed to find an association between use of LSD and rate of birth defects (Grof 2000: 1980). It thus appears that LSD is neither mutagenic nor teratogenic. Some ergolines have been used to induce labor, and there is limited evidence that LSD might promote contractions in uterine tissue (Zhang and Dyer 1993). Reproductive risks can be prevented or eliminated through restricting enrollment to women who are not pregnant or lactating and who are using an effective means of birth control.

Research trial data

None gathered at present; there are no current ongoing or published studies of LSD.

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