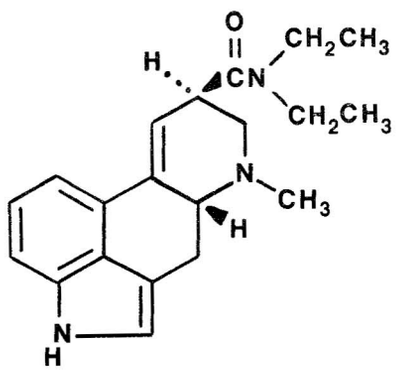
Profiles of Psychedelic Drugs



9. LSD

Description and Properties: LSD-25, N,N-diethyl-*d*-lysergamide, 9,10-didehydro-N,N-diethyl-6-methyl ergoline-8(β)-carboxamide, Delysid®, is a white, base-unstable crystalline solid, m.p. 80-85° from benzene or isopropyl ether. It forms a tartrate salt containing methanol of crystallization, m.p. 198-200° with decomposition. LSD in solution, either as the free base or as the salt, is rapidly decomposed in light.

History: The ergoline alkaloids come from two botanical sources, both with a long psychopharmacological history. Fungal growths of the genus *Claviceps* parasitize various grains and grasses, and are believed to be the basis of the visionary intoxication of the Eleusinian rites of classical times, and the toxic factor in spasmotic ergotism (St. Anthony's Fire) of the Middle Ages. In the New World, the seeds of several Convolvulaceae (morning glories such as *Ipomoea violacea* and *Rivea corymbosa*) have been employed for centuries as a magic potion and divinatory sacrament under the name Ololiuqui. The fundamental backbone of most of the ergot-like alkaloids present in these botanicals is lysergic acid, which was first converted to the diethylamide derivative (LSD) in 1938. The remarkable psychotropic potency of this base was noted in 1943, and in the following decades it has become the most thoroughly studied of all the psychedelic drugs.

Biochemistry and Pharmacology: LSD is intimately involved with both the serotoninergic and dopaminergic systems of neural transmission. In tissues outside of the central nervous system (CNS) it blocks the action of serotonin similarly to its 2-bromo derivative (BOL) which is without psychedelic effectiveness. Within the CNS however, it is much more effective in increasing serotonin levels through blocking of the brain neurons that employ this neurotransmitter. Here, also, it mimics dopamine in its actions. Most structural modifications dramatically reduce the potency of LSD. The three possible optical isomers of *d*-LSD (the enantiomorph *l*-LSD and the diastereoisomeric pair *d*-iso-LSD and *l*-iso-LSD), addition to the piperidine-ring double bond (hydrogenation to dihydro-LSD or water addition through light exposure in solution to lumi-LSD) or substitution at the pyrrole 2-position are all devoid of psychedelic activity. Variations of the alkyl groups on the amide nitrogen lead to homologs of lower specific activity. It is only with the metabolically labile substituents on the indolic nitrogen (hydroxymethylation to give OML-632, acetylation to give ALD-52) that the parent compound's potency is largely maintained. LSD is rapidly and extensively metabolized in humans through both disruption of the amide group and through aromatic hydroxylation. The kinetics of serum levels approximate the psychological chronology, with a maximum level seen in about an hour and a subsequent half life of three hours.

Human Psychopharmacology: The usual effective dosage of LSD, orally, is in the range of 50-150 micrograms. Intramuscular administration requires the same dosage, the intravenous route needs slightly less material with effects noted in a very few minutes. Studies employing intraspinal administration have used about one-third the usual dosage and led to virtually instantaneous responses. The effects usually develop from the 40-minute point to about one and one-half hours following oral administration, although occasionally an early, rapid onset is experienced (starting at 15 minutes and completely developed within the hour). Some

psychological aspects of the intoxication are consistently experienced: visual misinterpretation (colors, shapes and character of objects), distortion of time sense, and depersonalization. Other subjective effects depend largely on the set of the subject and the environment of the experiment, and reflect the anxieties, expectations or personal problems at hand. The overall character of the experience can be hilarious, erotic, introspective or overwhelmingly frightening, and need not be consistent from experience to experience. Recovery from the peak of intoxication is noted at about the fourth hour and is usually complete in another four hours. Subsequent appetite and sleep are normal in most individuals. Short-term tolerance to repeated exposures is developed, and lost, rapidly.

Legal Status: LSD and its precursor lysergic acid are listed in the Federal Controlled Substances Act as Schedule I and Schedule III drugs, respectively, with registry numbers 7315 and 7300.

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