Clinical Aspects of Use of Phenylalkylamine and Indolealkylamine Hallucinogens

Leo E. Hollister, M.D.[1]

Scarcely any clinical studies of hallucinogens have been reported since 1968. A variety of reasons account for this diminution of interest. Much of the information about clinical effects, potential therapeutic uses, and adverse effects must be gleaned from older work (Hollister, 1968).

Mescaline is the prototypic phenylalkyl amine hallucinogen. Others include 2,5-dimethoxy-4-methyl amphetamine ("STP") and methylene-dioxymethamphetamine (MDMA). Lysergic acid diethylamide (LSD) and psilocybin are the prototypic indolealkylamine hallucinogens, which also include N,N-dimethyltryptamine and bufotenin. Aside from great differences in potency (1 µg LSD equals 225 µg psilocybin equals 5 mg mescaline), the clinical syndromes produced by these three drugs are virtually identical. Somatic symptoms include dizziness, weakness, tremors, nausea, drowsiness, paresthesia, and blurred vision. Perceptual changes include altered shapes and colors, difficulty in focusing on objects, sharpened sense of hearing and, rarely, synesthesias. Psychic manifestations include alterations in mood, tension and, rarely, hallucinations. The usual doses, in terms of LSD, to produce such effects range from 50 to 200 µg. No fatal overdoses have been recorded. The usual duration of drug effect is about 6 to 8 hours, or longer with higher doses.

Various claims have been made for therapeutic utility of these drugs in alcoholism, depression, schizophrenia, neuroses, and psychopathy. The drugs have been averred to facilitate insight psychotherapy, to provide a "mock death," to create religious experiences, and to promote better interaction in group psychotherapy. None of these claims has ever been validated experimentally. That claim most often studied, beneficial effect of LSD for treating alcoholics, has never been confirmed.

Acute panic reactions are the most common adverse effect, but are of limited duration. Depression and psychosis may be precipitated by the drug but are not created de novo. Thus, these drugs have failed to produce a valid model psychosis. "Flashbacks" are still of uncertain cause. Injury to self, and occasionally a homicide, are related to lack of judgment and/or disinhibition.

The major current concern is about the fad drug, methylene-dioxymethamphetamine (MDMA). This phenethylamine derivative was first synthetized many years ago but is not as well known or as well studied as methylene-dioxyamphetamine (MDA). The latter drug was one of many phenethylamine hallucinogens of interest to the U.S. Army as part of its studies of "incapacitating agents." A study of this drug at a major medical center during the early 1950s came to an abrupt halt with the death of one of the subjects. He had been given a dose of around 30 mg without much effect. Other subjects had received higher doses of related compounds. When he received the second dose of about 460 mg (6 mg/kg), he experienced muscle spasms, seizures, and cardiovascular collapse. The dose of 6 mg/kg had been predicted as potentially lethal based on toxicological studies.

In the late 1950s, Gordon Alles ran a series of clinical trials in which MDA was compared with amphetamine at doses ranging from 60 to 120 mg. At the highest doses, distinct visual and other sensory changes (increased auditory sensitivity and alterations in peripheral vision) were noted, but no hallucinogenic effects (Alles, 1959). In 1967 Alex Shulgin and collaborators reported on 8 subjects who received doses up to 150 mg. These subjects, who were well experienced with other LSD-type hallucinogens, reported no hallucinations, perceptual distortions, or eye-closed

[1]Veterans Administration Medical Center (151H), 3801 Miranda Avenue, Palo Alto, CA 94304.

imagery, all of which are very common reactions to LSD-type drugs. Similarities between MDA and LSD-type drugs were intensification of feelings, increased perceptions of insight, and heightened empathy with others. Most subjects also reported increased esthetic enjoyment. Effects appeared within 40 to 60 minutes of ingestion, peaked in about 90 minutes and had largely dissipated by 8 hours, a time course comparable to that of LSD-type drugs. It was concluded that MDA was not classifiable as a hallucinogen but rather was unique in producing an "inward, talky experience" (Naranjo et al., 1967).

Shulgin's group reported a few years later on 3-methoxy-4-,5-methylene-dioxyphenyl–isopropylamine (MMDA), a related compound. Clinical effects were similar to those from MDA, without true hallucinogenic effects. It, too, was deemed useful for psychotherapy. Rather low toxicity was found in rats, with a therapeutic index (LD_{50} rats/MED_{50} humans) to be 85, rather high. Striking hypotension was noted in dogs, however, indicating species differences in response (Shulgin et al., 1973).

A 1970 report on MDA confirmed the time course of the drug's effects. Subjects experienced a mild sense of physical well-being, increased taste sensation, decreased awareness of bodily sensations, and increased need for interpersonal relationships. Several short visual hallucinations were experienced by one subject. Physical exhaustion and free-floating anxiety which lasted up to 2 days were the usual sequelae (Jackson & Reed, 1970).

The potential lethality of MDA in overdose was again confirmed by a 1983 report. A subject who had taken a dose of about 500 mg experienced a tonic seizure followed by coma some 15 minutes after ingestion. Tachycardia, rapid respirations, and slight hypertension were noted. The pupils became dilated and fixed, sweating and piloerection were observed, the extremities became rigid along with trismus, and respiratory depression followed. The subject eventually recovered. Two other users of the drug had similar, though milder reactions (Richards & Borgstedt, 1971).

Another disconcerting aspect of the MDA story is that a recent study in animals suggests that it is a neurotoxin specific for serotonergic pathways in the brain (Ricuarte et al., 1985). The full implications of this observation are not at all clear. A similar observation has suggested that fenfluramine is also a serotonin neurotoxin, yet this drug has been widely used in clinical practice without any evident adverse neurological consequences.

It is conceivable that MDA is not truly a hallucinogen. Substitution of the aromatic portion of the molecule at the 3 and 4-positions is usually not adequate for producing hallucinogenic effects. Thus, the contention that MDA is not truly a hallucinogen but more closely related to amphetamine may be correct. The story with MDMA as reported by those therapists who use it sounds much the same. They report the same sort of empathetic experiences in their patients without major hallucinogenic actions. It would be surprising if MDMA were to be markedly different from MDA. Usual doses used in therapeutic sessions are around 200 mg, about 50% of the potential lethal dose. In contrast, a lethal dose of LSD has not yet been determined.

We should be hearing much more about MDMA, for some entrepreneur is funding studies of the drug directed towards a New Drug Application. He envisions a chain of clinics in which this drug would be used to facilitate psychotherapy. Specially trained "therapists," not necessarily physicians, would monitor the therapy. If MDMA is commercialized it would be the first such instance for a hallucinogen.

The 4-bromo homolog of 4-methyl,2,5-dimethoxyamphetamine (DOM, STP) has appeared in some countries as a street hallucinogen under several names including DOB or bromo-DMA (Delliou & Bromo, 1980). Shulgin had reported that in doses of 2 mg it resembled MDA. Even doses of 3 mg have been associated with convulsions, attesting to its much greater potency than DOM. Further, the Br substituent delays metabolism, so effects of this drug are prolonged.

Two young persons were poisoned by DOB. A young woman who had ingested what was believed to be 30 to 35 mg died after seizures and cardiovascular collapse. Postmortem finding included evidence of increased intracranial pressure and acute pulmonary congestion. Her companion, a young man poisoned with an unknown amount of this drug, experienced repeated convulsions and prolonged coma with permanent brain damage (Winek et al., 1981).

An unusual effect of DOB is the production of marked, diffuse, and progressive peripheral arterial vasospasm. A 33-year old man had taken an unknown amount of DOB several hours before the onset of cold extremities. Pulses were absent and spasm was demonstrated on subclavian angiograms. Vasodilators were used with reversal of the vasospasm in 24 hours. An earlier instance of vasospasm after a putative dose of 75 mg of DOB resulted in bilateral above-the-knee amputations. It is possible that the cerebral effects of overdoses of this drug are also associated with vasospasm (Bowen et al., 1983).

These two new phenethylamines have serious potential side effects, including death. Although no deaths have been directly attributed to MDMA, experience with MDA strongly suggests this possibility. Some trismus and muscle spasms have been noted even in subjects who received 200 mg "therapeutic" doses of MDMA. Thus, doses usually used in therapeutic sessions with this drug are perilously close to those that have been lethal. As it is not always certain that doses of street drugs can be accurately determined, a relatively minor error in dose could have serious consequences.

Whether MDMA will, despite its evident hazards, prove to be the panacea for psychotherapy claimed by its adherents remains to be seen. The present claims are exactly the same as those made by many of the same persons about LSD 20 years ago. The difference is that LSD has a remarkable margin of safety, something lacking in the newer agents.

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