



## Review Article

## Is LSD toxic?

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## ABSTRACT

LSD (lysergic acid diethylamide) was discovered almost 75 years ago, and has been the object of episodic controversy since then. While initially explored as an adjunctive psychiatric treatment, its recreational use by the general public has persisted and on occasion has been associated with adverse outcomes, particularly when the drug is taken under suboptimal conditions. LSD's potential to cause psychological disturbance (*bad trips*) has been long understood, and has rarely been associated with accidental deaths and suicide. From a physiological perspective, however, LSD is known to be non-toxic and medically safe when taken at standard dosages (50–200 µg). The scientific literature, along with recent media reports, have unfortunately implicated “LSD toxicity” in five cases of sudden death. On close examination, however, two of these fatalities were associated with ingestion of massive overdoses, two were evidently in individuals with psychological agitation after taking standard doses of LSD who were then placed in maximal physical restraint positions (*hogtied*) by police, following which they suffered fatal cardiovascular collapse, and one case of extreme hyperthermia leading to death that was likely caused by a drug substituted for LSD with strong effects on central nervous system temperature regulation (e.g. 25i-NBOMe). Given the renewed interest in the therapeutic potential of LSD and other psychedelic drugs, it is important that an accurate understanding be established of the true causes of such fatalities that had been erroneously attributed to LSD toxicity, including massive overdoses, excessive physical restraints, and psychoactive drugs other than LSD.

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## 1. Introduction

Lysergic acid diethylamide (LSD) is a semi-synthetic natural product derived in nature from the rye fungus, *Claviceps purpurea*. It was first synthesized in 1938 by Swiss chemist Albert Hofmann, who was at that time exploring the putative medicinal effects of a

series of ergot derivatives. Hofmann, five years later in 1943, accidentally discovered the unique psychological effects of the compound he identified as LSD-25, which he found was profoundly psychoactive at remarkably low microgram level doses. From the early 1950s, through the 1960s considerable clinical research activity with LSD raised hopes and enthusiasm that a valuable new treatment tool would be available to psychiatrists and other mental health professionals, particularly for use in cases that were refractory, or treatment resistant, to the standard mainstream approaches of that time. In all, about 1000 clinical case reports were published from the early 1950s through the 1960s, discussing

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treatment of approximately 40,000 subjects, mostly with LSD [1]. Comprehensive reviews of clinical outcomes of experimental LSD studies conducted in the United States and the United Kingdom during the 1950s and 1960s identified very low rates of adverse effects [2–4]. FDA-approved clinical studies of LSD ended with the passage of the controlled substances act (CSA) of 1970. Recently, however, controlled clinical studies have been resumed in Europe, although not as yet in the United States [5–12].

Although LSD is now classified as a Schedule 1 drug with no safe or recognized therapeutic use, its informal use by the public has continued over the past 50+ years [13,14]. Of particular note, however, is that reports of psychological adverse events outside of formal and approved research settings have notably declined over the past several decades. That is likely attributed to use of lower doses, access to better and more accurate information, improved psychological preparation, and greater attention given to supportive environmental conditions.

Experts now generally recognize that LSD is an extremely physiologically safe substance, when moderate dosages are used (50–200 µg) in controlled settings, with only modest elevations of blood pressure, heart rate, and body temperature noted [8,15,16]. It is estimated that 10.2% of the current U.S. population has ever taken LSD [17], giving an estimate that approximately 31 million people have ever used LSD, with not a single documented death due to LSD at recreational doses [17–19].

Although fatalities after LSD use can occur when the intoxication leads the user to carry out dangerous activities such as walking across a busy highway, attempting to swim, rock climbing, etc., there are only two documented cases where LSD presumably directly led to fatality. In both cases, post-mortem analysis indicated that the decedents had ingested massive doses of LSD.

## 2. Deaths associated with LSD

Gable [20] estimated that the lethal oral dose of LSD in man is 14 mg, based on the reported LD50 in rabbits and one elephant. He later [21] revised his estimate of the lethal blood concentration based on mouse and rat studies as 4.8 µg/mL, and revised the lethal oral dose of LSD in humans to be 100 mg, citing Griggs and Ward [22] that a fatal LSD dose ingested was equivalent to 800–1600 times the usual street dose then of 200–400 µg. In the case report described by Griggs and Ward [22] the liver concentration of LSD was reported as 31.2 µg/mL (31,200 ng/mL). They extrapolate, based on a study in cats, that the decedent in this case may have received an LSD dose equivalent to about 320 mg intravenously, or “23 times the previously calculated lethal human dose.”

In a case reported by Fysh et al. [23], the cause of death was stated to be poisoning by LSD, but sufficient details are lacking to determine the actual dose ingested. In that report, a 25-year-old male died 16 h after being admitted to the hospital, but it is not reported how much earlier his LSD ingestion occurred. Analysis of ante-mortem serum gave 14.4 ng/mL, but if analysis of his plasma had been carried out more proximal to his ingestion of the drug, this concentration would have been much higher.

These latter two cases document death by LSD overdose, but only from massive doses of drug that might be available directly from a manufacturer, and not from a typical distributor of recreational dosage forms such as blotters or liquid solutions.

Even so, heroic doses of LSD can be ingested without fatality when supportive hospital care is readily available. Klock et al. [24] report on massive LSD overdose in eight patients who nasally insufflated pure LSD tartrate powder, believing it to be cocaine. They were admitted to the emergency room within 15 min after insufflation. Five patients were comatose, and most were extremely hyperactive with severe visual and auditory hallucinations. All had sinus tachycardia, widely dilated pupils, emesis,

flushing, and sweating. Fever developed in four and diarrhea in two. Transient hypertension was present in three patients but no patient had convulsions. Specimens of blood were obtained on admission. Blood concentrations of LSD were measured for four patients as high as 26 ng/mL. Gastric concentrations of LSD were as high as 7.0 mg/100 mL (or 70,000 ng/mL). After supportive therapy all eight patients fully recovered within 2–3 days.

Fatality also has occurred when LSD users were having a “bad trip” and were subsequently restrained with hog-tying type restraint. In a report by O'Halloran and Lewman [25] a 14-year old boy reportedly on a bad LSD trip jumped through a window and cut his leg. He was screaming obscenities, talking incoherently, and spitting. Police were called and it took four adults to restrain him and transport him to the hospital emergency room. His constant struggling prevented attempts to suture his lacerations. He was placed prone on a hospital gurney with his hands cuffed behind his back, and was transported three blocks to a juvenile detention center. Still struggling and spitting, he was placed in soft restraints *and hogtied*. Manual pressure was applied to his back and shortly thereafter he went limp. After being carried to a padded room and placed prone on the floor, within a minute he was discovered to be unconscious and not breathing. He was rushed back to the hospital where he died after seven days in a coma. Tests of admitting blood samples from the hospital were positive only for LSD. The authors of this report considered it to be death due to restraint asphyxiation in “excited delirium.” We shall return to the notion of excited delirium later in this discussion.

In a case described by Reay et al. [26] a victim was a 28-year-old healthy male who was house sitting and drinking beer with his brother most of one afternoon. Later, the brothers went out to their van for a trip to the store, noticed that someone had tampered with their van, and began shouting at each other. Neighbors assumed they were fighting and called police. Two police officers arrived and tried to calm the brothers and get them to go into their house. At some point, a records search found outstanding traffic warrants on the victim. The victim would not quiet down and became increasingly agitated. When faced with the option of going into the house or being arrested, he ran. A pursuit and struggle ensued. He was struck several times with nightsticks, once to the head. After the victim was partially subdued prone on the ground, a witness to the event ran out and held the victim's legs. Several officers arrived to help restrain and hogtie the victim. Once the victim was finally restrained, and while still resisting and complaining, he was placed in a prone position in the back of a patrol car on a narrow, molded plastic, one-piece seat. While en route to the jail, the victim slipped down and became wedged between the front and back seats with his left shoulder partway up the back of the front seat and his right shoulder against the bottom panel and foot well of the back seat. About three min later, his breathing was “gurgly” and the transporting officer called a Code 3 upgrade to paramedics. Medics arrived at the jail about the same time as the officer and victim. Approximately 4 min had elapsed during the trip from the scene to the jail. The victim was unresponsive when removed from the patrol car. Despite all efforts, he never regained any vital signs and was pronounced dead. Toxicologic tests found a blood alcohol level of 0.12 g/100 mL, a LSD blood level of 3.2 ng/mL, a THC blood level of 4.1 ng/mL, and THC blood metabolite level of 108 ng/mL. No other drugs or chemical findings of note were present. Death was attributed to positional asphyxia.

Most recently, two deaths have been attributed to LSD toxicity. The first case is that of a 30-year-old male with a history of asthma but no other significant past medical history. According to his wife, he ingested a small quantity of LSD, after which he became frightened and claustrophobic. He ran approximately a quarter mile through a commercial area and a bystander contacted police to report his erratic behavior. Upon arrival, police ordered a K-9

unit to subdue the patient, which bit him on the left arm. Police then fired a taser at the patient, striking him in the back. Multiple officers then physically restrained him, with one officer straddling the patient's back. The patient was placed in a hog-tie position, in which the patient's hands and feet were shackled and connected together behind his back.

EMS arrived and the patient was placed prone on a stretcher. The patient's hands and feet were still restrained as described above and five sets of straps were placed across his body, including his head, securing him to the stretcher. He visibly struggled against the restraints. EMS took vital signs, including a 3-lead ECG that showed the patient had supraventricular tachycardia with decreasing diastolic blood pressure. At 2024, EMS checked lung sounds, which did not reveal any evidence of fluid in the lung fields.

The patient arrived at the hospital at 2033, and four minutes later was tachycardic at 164 beats per minute and tachypneic at 24 breaths per minute with SpO<sub>2</sub> of 90%. His blood pressure was 122/64 and his temperature was reported as 98.2°F. The patient remained restrained and continued struggling against restraints. He was administered haloperidol and lorazepam at 2108. At 2122, police reported to hospital personnel that the patient had become unresponsive. Restraints were removed and Advanced Cardiovascular Life Support (ACLS) protocol for pulseless electrical activity was followed for 22 min. The patient was administered multiple rounds of epinephrine, sodium bicarbonate, sodium chloride, and Narcan without improvement. The patient had one episode of ventricular fibrillation with cardioversion/defibrillation resulting in pulseless electrical activity and asystole. The patient was pronounced dead at 2144 with asystole, no respiratory effort, and no palpable blood pressure.

The toxicology report indicated 1 ng/mL of LSD in post-mortem subclavian blood, as well as tetrahydrocannabinol, but with no other drugs detected, which included analysis for several NBOME type compounds, as well as synthetic cannabimimetics. The medical examiner reported the cause of death “a result of complications of LSD toxicity.”

There is absolutely no evidence in the medical/scientific literature that this plasma concentration of LSD is toxic, or would be consistent with the size of LSD overdose that might result in death. Indeed, as seen in Fig. 1, a plasma LSD concentration of 1 ng/mL at five hours after drug ingestion would suggest that the decedent had initially ingested only about 100 µg of LSD.

In the second recent case, a 20-year-old female was attending a music festival in California. She was believed to have taken LSD. Importantly, the decedent had temperatures of 105° prior to arrival

at the hospital and 103° while being treated in the hospital. It should be pointed out that extreme hyperthermia is *not* consistent with LSD intoxication. Approximately 4800 mL of fluid were removed from the decedent's lungs at the hospital. Two samples of postmortem subclavian blood were analyzed to contain 0.22 ng/mL and 0.47 ng/mL, consistent with ingestion of no more than one recreational dose of LSD (see Fig. 1). Specific drug assay for bath salts, GHB, LSD, MDMA, psilocin, synthetic cannabimimetics (“spice compounds”), and U-17700 revealed only LSD; no ethanol was present. No other drugs were detected. In the initial Coroner's Report of June 16, 2017, death was attributed to “Acute LSD Toxicity.”

Unfortunately, the list of drugs included in the assay performed by the Toxicology laboratory did not include drugs likely to have caused hyperthermia and known to be associated with lethality, such as 25i-NBOMe [27–29], para-methoxyamphetamine (PMA) [30], or its *N*-methyl derivative PMMA [31]. Thus, the conclusion of death by “Acute LSD Toxicity” is extremely dubious, to say the least. In response to press reports questioning that cause of death, the autopsy report was updated on September 12, 2017 to indicate the cause of death as multi organ failure, hyperthermia, and dehydration, with coagulopathy and possible LSD intoxication. There was no report of further blood analysis to determine what drug was actually responsible for the symptoms that preceded death.

According to Cina [32] “most anecdotal and clinical evidence suggests that persons who suddenly collapse during vigorous restraint suffer from lethal cardiac dysrhythmias (though other mechanisms such as respiratory arrest may predominate in some cases).” These authors suggested that the term Cardiac Dysrhythmia During Restraint (CDDR) may be the most intellectually honest cause of death in challenging cases.

It will be instructive to consider what blood concentrations of LSD are achieved after administration of a typical dose of LSD so that future deaths will not be misattributed to LSD toxicity. Upshall and Wailling [33] orally administered 160 µg of LSD tartrate to 13 human subjects and examined the plasma concentration of LSD after a full meal, no meal, or a light meal. The average plasma concentration of LSD in eight subjects after a light meal was 3.19 and 4.16 ng/mL 60 and 130 min after administration of LSD, respectively.

A recent study of LSD pharmacokinetics was reported by Dolder et al. [34], with similar results. They administered a single oral dose of 200 µg of LSD (free base) to 16 human subjects and then determined the plasma levels of the drug at various times after drug administration. This dose, corrected for the tartrate salt, which is the dosage form most often distributed, would be equivalent to 246 µg, considered to be a larger dose than is typically available today. In a subsequent study, Dolder et al. [16] examined the pharmacokinetics of LSD after administration of 100 µg of LSD free base (equivalent to 123 µg of LSD tartrate). In addition, they reanalyzed their 2015 study data to determine more accurately plasma concentrations after the 200 µg oral dose of free base. In both studies, the  $t_{1/2}$  of LSD was reported as 2.6 h, with a  $C_{max}$  of 1.3 and 3.1 ng/mL, and a  $t_{max}$  of 1.4 and 1.5 h, respectively, for the 100 and 200 µg doses. The plasma concentration–time curves for both doses are illustrated in Fig. 1.

In the cases described here for deaths following recreational use of LSD, in three cases the decedents exhibited signs of agitation and were all placed in the position of prone maximal restraint (PMR; hogtied). In the first case, discussed by O'Halloran et al. [25], the cause of death was restraint asphyxiation in “excited delirium.” In the fourth case the cause of death is questionable because the plasma concentrations of LSD were too low, and because the forensic laboratory did not test for drugs that were likely to cause death.

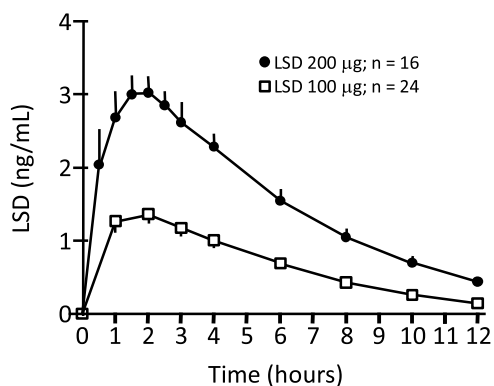


Fig. 1. Blood plasma concentration of LSD after oral doses of 100 or 200 µg of LSD free base in human volunteers. Adapted from Dolder et al. [16].

There has been considerable debate about whether or not PMR can cause death, and that literature will not be reviewed here. Some recent studies, however, have attempted to show that PMR is not dangerous. Savaser et al. [35] studied the effect of the prone maximal restraint position with or without 50- or 100-pound weights applied to the back on measures of cardiac function including vital signs, oxygenation, stroke volume (SV), IVC diameter, cardiac output (CO) and cardiac index (CI). They employed 25 healthy male volunteers. Notably, the time of restraint was only three minutes, with subjects allowed a five-minute rest between tests. They reported that PMR with and without weight force did not result in any changes in CO or other evidence of cardiovascular or hemodynamic compromise, implying the relative safety of PMR. Nonetheless, it seems doubtful that the results of these experiments can be taken too seriously because of the short time the subjects were restrained, in addition to the fact that the subjects were not in an agitated or excited state.

The term “Excited Delirium” refers to a subcategory of delirium that has primarily been described retrospectively in the forensic literature. First described by Wetli and Fishbain [36], it presented as fatal cocaine intoxication, where subjects had acute and intense paranoia, followed by bizarre and violent behavior requiring forcible restraint. Fatal respiratory collapse occurred suddenly and without warning, generally within a few minutes to an hour after the victim was restrained.

Excited delirium also has been referred to as “Agitated Delirium” and is closely associated with the “Sudden Death in Custody Syndrome” [37,38]. The 1980s saw a dramatic increase in the number of reported cases with behavior similar to an uncontrolled psychiatric emergency. Most of these cases were associated with the introduction and abuse of cocaine. Excited Delirium Syndrome (ExDS) has now been recognized to occur in association with illicit drugs of abuse other than cocaine, particularly methamphetamine and PCP. Although Vilke [37] cites two references (24 and 25 in Vilke) that supposedly indicate that LSD also can cause ExDS, in fact there is no mention of LSD in either of those references.

Key features of ExDS include insensitivity to pain, tachypnea, sweating, agitation, profound hyperthermia, non-compliance with police, severe agitation and combative or assaultive behavior, lack of tiring, unusual strength, inappropriately clothed, and mirror or glass attraction. Subsequent postmortem brain examination demonstrated a characteristic loss of the dopamine transporter in the striatum of chronic cocaine abusers who die in police custody from apparent ExDS (see references in Ref. [37]). Thus, it has been speculated that one potential pathway for the development of ExDS could be excessive dopamine stimulation in the striatum, but the significance of that finding in the larger context of ExDS unrelated to chronic cocaine abuse is unclear. Acute use of LSD stimulates primarily serotonin 5-HT<sub>2</sub> receptors [39] and would not be expected to act on the dopamine transporter or result in loss of striatal dopamine.

It is well known that some LSD users can experience what is called a “bad trip.” A bad trip usually presents as acute and severe anxiety, often accompanied by fear and agitation, with varying degrees of delusional or paranoid thinking. How much overlap is there between the symptoms of a bad trip and the ExDS? Individuals experiencing a bad trip under LSD usually do not share the aggressive violent behavior manifested by subjects with ExDS, although they may be noncompliant with police. Furthermore, acute LSD intoxication typically does not lead to extreme hyperthermia, although LSD does very modestly elevate body temperature [8]. Certainly some of the symptoms of a bad trip could include tachycardia and sweating, and other symptoms of sympathetic nervous system activation as a result of intense fear/anxiety. In addition, some individuals experiencing the ExDS may

suddenly die [40], whereas there are no cases reported of LSD bad trips leading to fatality. In the cases cited above, where the subjects intoxicated with LSD subsequently died, in each case they had been restrained using PMR. Hence, it may be reasonable to conclude that PMR can lead to fatality in persons having a bad LSD trip.

Hall et al. [40] collected data from August 2006 until March 2013, representing 4828 consecutive use of force events in seven Canadian police agencies in four cities. Overall, there were 499 individuals in the entire cohort with three or more concomitant features of excited delirium at the time of the use of force event, and within that group, 86 individuals had six or more concomitant features. The incidence of sudden in-custody death for their consecutive use of force cohort in whom the final position was known was 1/4373 or 0.02%, with a 95% CI of (0.0005, 0.1%). From their data, the 95% confidence intervals indicate that, in a worst-case scenario, 99.8% of subjects would be expected to survive being in either the prone or not prone position following a police use of force event. In their study, the only subject who died was in a not-prone position. The person who died exhibited all 10 features of excited delirium during the police use of force event, including being partially clothed, destroying glass, failing to respond to police presence, demonstrating constant physical activity, failing to tire despite heavy physical activity, having unexpected strength, being unaffected by pain, rapidly breathing, being hot to the touch, and having excessive sweating.

It has been suggested that subjects in a state of excited delirium are more susceptible to positional asphyxia due to a need to hyperventilate in order to compensate for an underlying acidosis. However, deaths in excited delirium cases have been described after hogtie positioning, prone positioning, supine positioning and chemical restraint. In short, the effect of position following restraint in this population remains unclear. Their data do not support the notion that prone positioning is specifically dangerous either as “positional asphyxia” or its hybrid “restraint asphyxia.”

Most importantly, it should be emphasized that, unlike other cohorts, no individual in their cohort had ankle and/or leg restraints connected in a hogtied fashion. They conclude with this statement, “We cannot comment on the effect of the position of maximal restraint since it was not employed by any agency during the course of our study” [40]. Although there is controversy over what causes excited delirium syndrome, as well as debate about the role of the position of maximal restraint, the fact of the matter is that when arrestees are not hogtied, they typically do not die.

More often, police come into contact with the deceased during the phase of psychotic agitation, just as death is about to occur. A struggle will ensue, and chemical incapacitating agents, capicum spray in the US or CS spray in the UK, may be employed with no effect. In the average case, the concerted efforts of five or six officers will be required to force the victim to the ground and apply restraints. Respiratory arrest tends to occur shortly after the restraints are applied, while the victim is on the ground or being transported [41].

### 3. Conclusions

In conclusion, LSD does not have the degree of physiological toxicity alleged by recent reports in the professional literature and in the media. These reports have caused confusion by distracting from what is likely the true causes of these reported deaths, excessive physical restraints and/or psychoactive drugs other than LSD. Furthermore, given recent increased interest in psychedelics (including LSD) used as part of a discrete treatment model, particularly for refractory psychiatric disorders [11,42,43], we need a clear and accurate understanding of the drug’s genuine toxicity, which in humans has consistently been demonstrated to be very low.

## Author statements

Both authors contributed equally to the writing of this manuscript, and both authors have approved the final article.

## Conflict of interest

The authors declare no conflicts of interest.

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