

Neurotoxicity and LSD treatment: a follow-up study of 151 patients in Denmark

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Abstract

LSD was introduced in psychiatry in the 1950s. Between 1960 and 1973, nearly 400 patients were treated with LSD in Denmark. By 1964, one homicide, two suicides and four suicide attempts had been reported. In 1986 the Danish LSD Damages Law was passed after complaints by only one patient. According to the Law, all 154 applicants received financial compensation for LSD-inflicted harm. The Danish State Archives has preserved the case material of 151 of the 154 applicants. Most of the patients suffered from severe side effects of the LSD treatment many years afterwards. In particular, two-thirds of the patients had flashbacks. With the recent interest in LSD therapy, we should consider the neurotoxic potential of LSD.

Keywords

Denmark, LSD, LSD damages law, LSD therapy, LSD toxicity, psycholytic therapy, 20th century

Introduction

Lysergic acid diethylamide (LSD)-25 was synthesized in 1938 by the Swiss chemists Albert Hofmann (1906–2008) and Arthur Stoll (1887–1971). LSD, usually written without the lysergic acid derivative series number 25, has obtained doubtful notoriety in psychiatry and society.

In 1918 in the laboratories of the pharmaceutical company Sandoz in Basel, Stoll had isolated ergotamine from ergot, which was widely used in obstetrics and migraine treatment. Hofmann asked Stoll to continue the investigations on the alkaloids of ergot to examine the stimulating potential of the derivatives on respiration and blood circulation (Hofmann, 1980: 8–12). This work led to the discovery of LSD. After a few disappointing animal experiments, further testing was discontinued (Hofmann, 1980: 13).

Hofmann did not forget (LSD)-25, and on 16 April 1943 he produced a few centigrams of the compound to give to the pharmacological department for further tests. However, in the middle of the afternoon he had to interrupt his work and go home, where he ‘sank into a not unpleasant

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intoxicated-like condition, characterized by extremely stimulated imagination'. He 'perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colours. After some two hours this condition faded away ...' (Hofmann, 1980: 14).

Hofmann realized that during crystallization some of the LSD solution might have contacted his fingertips and been absorbed through the skin. On 19 April 1943, he decided to perform a self-experiment. He took a dose of 250 micrograms of LSD diluted in water and a half an hour later experienced a very serious reaction with vivid hallucinations, intense fear and despair, out-of-body experiences and intense mortal dread. After a good night's sleep, Hoffmann felt that he was in excellent physical and mental condition without a hangover and was able to remember the experience of the LSD intoxication in complete detail (Hofmann, 1980: 17).

The psychic effect of LSD, later designated as the psychedelic effect, was a surprise to Hofmann, as was the small amount of the active substance needed to cause the reaction (Hofmann, 1980: 17). Perhaps he should not have been surprised, for he was well aware of the origin of ergot from the fungus *Claviceps purpurea*, which grows on rye and other species of grain as well as on wild grasses. In the Middle Ages, outbreaks of mass poisoning with ergot-containing bread affected and killed thousands of people, and this had been well described. One of the names of this dreadful illness was 'St Anthony's fire' after the patron saint of ergotism prayers, and the order of St Anthony, which treated these patients (Alm and Elvevåg, 2013; Hofmann, 1980: 9; Siegel, 1985).

No one who sees the Issenheim Altar by Matthias Grünewald (c.1475–1528) in Colmar in Alsace can doubt that one of the figures, a man with severe ergotism, also suffered from terrifying hallucinations. However, at that time, the visions were interpreted as an assault by demons (Béguerie, 1991: 5; Nielsen, 1998: 111). This was also stated by Siegel (1985), who described hallucinations in the convulsive form of ergotism. Fuller (1968), in his account of the 1951 ergotism epidemic in France, described the presence of LSD-like hallucinations among the victims.

Hofmann wrote the foreword to a book on the history of 'St. Anthony's Fire in Art and Medicine', in which the neurotoxic potential of ergot was discussed (Bauer, 1973: 58). Hofmann said:

... from this research further drugs of great value have appeared; they are used in migraine treatment, in the treatment of circulatory disturbances and in geriatrics. Also drugs with such unusual effects as LSD have been found in this way. Ergot, once the cause of the feared Antonius-Fire, has thus changed from a poisonous substance into a rich gold mine of drugs ... (Bauer, 1973: 6)¹

LSD was marketed by Sandoz in 1947 and reached psychiatry in the 1950s. By 1965, the Sandoz company had requested that LSD should no longer be registered (Larsen, 2013: 229). It was withdrawn from the market in the mid-1960s and is now classified as a narcotic substance with severe potential of abuse. In Denmark, however, it could still be used scientifically until 1974.

In the late 1940s and 1950s, LSD was widely used to unravel the connection between behaviour and pharmacology, and early on it was often recommended as an aid to psychotherapy (Bernstein, 1988: 509). In this climate, Sandoz made the new substance available to research institutes and physicians as an experimental drug for the following purposes (Hofmann, 1980: 31):

1. Analytical psychotherapy,² to elicit the release of repressed material and provide mental relaxation, particularly in anxiety states and obsessional neuroses.
2. Experimental studies on the nature of psychoses: by taking LSD himself, the psychiatrist is able to gain insight into the world of ideas and sensations of mental patients. LSD can also be used to induce model psychosis of short duration in normal subjects, thus facilitating studies on the pathogenesis of mental disorder.

Although the idea of the LSD reaction as a model for psychosis was rejected soon after it was proposed, psychoanalysis took LSD into its practice to accelerate the therapeutic process (Larsen, 2013: 258). In psychoanalytical circles, it was generally believed that certain drugs were able to evoke unconscious material; therefore, this material became available for interpretation and therapy. As late as 1964, the official Danish psychiatric textbook stated: 'By using LSD, the patients may develop a psychotic-like state, in the process of which they reveal a lot of pathogenic material' (implying that this material may be a target of psychotherapy) (Strömngren, 1964: 242; see also Larsen, 2013: 224).

In Scandinavian countries, the centres of Modum Bad in Norway and Frederiksberg Hospital in Denmark became the leading centres of LSD research. Despite international warnings (Grinker, 1963; Rinkel, 1966) and the observation of serious side-effects, such as homicide, suicides and suicide attempts, especially in Danish reports (Geert-Jørgensen, Hertz, Knudsen and Kristensen, 1964), the attitude towards LSD treatment in the two centres remained positive or even enthusiastic (Geert-Jørgensen, 1968; Johnsen, 1967). Additionally, the development of persistent hallucinations, possibly of toxic origin, following repeated administration, as reported by Rosenthal (1964), seemed to have gone unnoticed at the two Scandinavian centres. It was reported in the Danish study that: 'Complications have been few and it seems absurd to have them tabulated.' It was, however, mentioned that:

... a few patients had brief episodes of after-effects repercussion several months after the treatment had terminated, either in the form of a revival of the LSD séance or as groundless fear – in a few isolated cases ... an already existing fear was seen to intensify some time after termination of treatment. (Geert-Jørgensen et al., 1964: 375)

This 1964 Danish study reported the results from a three-year period and included evaluations at three follow-up interviews (Geert-Jørgensen et al., 1964). The Norwegian report of the first 300 patients treated was evaluated many years later. The survey did not conclude that the LSD treatment had a decisive treatment effect. On the other hand, a low frequency of reported side-effects was found, which was considered to be a result of conscientious screening in the special therapeutic setting (Due-Madsen and Hoffart, 1996; Due-Madsen, Øyslebø and Hoffart, 1996).³

The Danish LSD treatment was never analysed again, until a special case 15–25 years later (see below) led to the collection of selected material on LSD-treated patients. Another 25 years has passed since this selected material became the object of analysis in the present study. Its purpose is: first, to evaluate the long-term outcome of LSD treatment in a population of Danish psychiatric patients; second, to estimate possible beneficial and damaging effects of the LSD-treatment; and finally, to find evidence for the possible neurotoxic potential of LSD.

Source material

From 1959 to 1973, nearly 400 patients were treated with LSD in Denmark, the majority at the Department of Psychiatry, Frederiksberg Hospital, one of the psychiatric departments in the Copenhagen area. During the same period, LSD treatment was also used in psychiatric departments and clinics throughout most of the country (Larsen, 2013: 250–1).

The case records from the 1960s and 1970s have not been preserved, and today it is not known exactly how many of the LSD-patients were treated at Frederiksberg Hospital or how many were treated as hospital patients or as private patients. However, it is most likely that one-third of the patients at Frederiksberg were treated as private patients.⁴ According to the Danish National Health

Service (NHS) in the 'Account of the course of the LSD-case 'in 1985, no attempt was made to elucidate this uncertainty.⁵ The major aim of the account was to establish that LSD treatment in Denmark was carried out as it was in other countries. For example, the Powick Hospital in England (Sandison and Whitelaw, 1954; Sandison and Whitelaw, 1954) was visited by Danish psychiatrists in the 1960s (Andersen, Kristensen and Knudsen, 1961; Vanggaard, 1964).

However, medical case records and other case material for 154 LSD-treated patients have been preserved, and the data for 151 of these patients are kept in the Danish State Archives. These were the patients who, under the LSD Damages Law of 1986, complained that they were harmed by the LSD treatment.

A single patient triggered the whole story. In 1961 a 23-year-old man visited the consultant psychiatrist at Frederiksberg Hospital. He was suffering from obsessions and compulsions, including painful washing rituals. After one year of psychotherapy without progress, LSD treatment was suggested to him and he accepted immediately. The first five treatments with 25 micrograms of LSD did not have any effect. Therefore, on 9 January 1962 the dosage was increased to 180 micrograms for the sixth treatment, which was going to be the last one. He then experienced a severe psychotic reaction with intense anxiety and later developed a chronic psychotic illness. His life became a tragedy; he went bankrupt in his profession as a farmer and was granted an invalidity pension (Larsen, 2013: 226). Many years later, from June to September 1987, he again experienced LSD treatment as a private patient of Professor Hanscarl Leuner (1919–96) in Tübingen, Germany. Although it was reported that the five test sessions with small but unknown dosages had a temporary beneficial effect, his mental condition soon deteriorated again. He was finally admitted to an American LSD specialist, Dr H. Abraham, who saw the patient on 2 May 2005, two days before he died at the age of 66 years. The result of Dr Abraham's evaluation was not kept.⁶

In 1972 this patient had sent a complaint about the LSD treatment to the Interior Ministry. The NHS, which is under the Interior Ministry, did not provide a response until the ombudsman became involved. On 20 December 1974, he said that he saw no reason to criticize the Interior Ministry and the NHS; however, he suggested taking a closer look at the LSD treatment at Frederiksberg Hospital to determine the actual course of events.⁷ Meanwhile, in 1974 the patient pressed charges against the responsible psychiatrists at Frederiksberg Hospital and the NHS because of the LSD treatments in 1961–62. In 1976 the Danish East High Court ruled against his contentions, and the judgment was not appealed to the Danish Supreme Court as the patient was not granted legal aid. Also, in 1988 he lost a trial against the medico-legal counsel.⁸ Three years after the decision in the Danish East High Court, on 30 May 1979, the ombudsman commented on this judgment and suggested consideration should be given to the question of public responsibility for harm that might be attributed to LSD treatment. Against the background of this suggestion, the Interior Ministry initiated further investigations; however, on 1 June 1983 it concluded that no reason was found to pay compensation for LSD-inflicted harm (Larsen, 2013: 253).

On 5 August 1983 a journalist from the Danish newspaper *Information* wrote about the state of affairs in psychiatry in an interview with the newly appointed Danish General Secretary of the World Psychiatric Association, Professor Schulsinger (1923–2012) (Larsen AF, 1983; Larsen, 2013: 225). The journalist, who at that time knew very little about LSD treatment, was contacted a few days later by the patient discussed above. He became professionally interested in the matter and consequently wrote many critical newspaper articles on the LSD treatment, as well as a book including his research on the history of the treatment (Larsen AF, 1985). The journalist was rewarded with the prestigious Cavling Prize in 1987 (Larsen, 2013: 226).

Meanwhile, the LSD treatment had become a matter of political discussion in Denmark and its Parliament; on 23 April 1986 the LSD Damages Law was passed, stating that patients treated with LSD could apply for reparatory compensation (LSD Damages Law, 1986). Under this law,

compensation can be given for LSD inflicted physical and psychological damage. Furthermore, treatment of the damage can be subsidized, whether it was to take place in Denmark or abroad. Section 1, subsection 2 of this law defines the so-called reversed burden of proof, stating: 'For harm, which is caused by or may be caused by treatment with LSD, this treatment is considered to be the cause (of the harm), unless it is most likely that the harm is due to another cause.'⁹ According to the law, applications for compensation had to be received by the Ministry of Social Affairs no later than 1 June 1988. On 28 May 1986, the NHS sent a circular to Danish medical doctors explaining how to apply for compensation: by completing a simple form allowing the applicant to give a short statement of the LSD treatment and the doctor to provide a short medical certificate.

Each application was dealt with by a tribunal under the Ministry of Social Affairs (the so-called LSD tribunal). The chairman was the permanent secretary of the Ministry of Social Affairs. The two ordinary members were the lay chairman of the Danish Society for Mental Health and the leading neurological consultant in the National Social Security Office. Thus, the LSD tribunal did not include psychiatric expertise (Larsen, 2013: 256).

A total of 176 applications were received, 19 of which were rejected as the information provided made it unlikely that these patients had been treated with LSD. Another three applicants were also rejected, two because they did not send in their application forms and one because the person realized that private use of LSD did not qualify for compensation under the law. As stated above, treatment of LSD-inflicted harm could be subsidized, and 12 of the applicants received free treatment: nine in Denmark and three abroad (Larsen, 2013: 257). Three applicants are still being treated; the case materials for these patients are kept in the National Industrial Injury Office but have not been made available to me.

Thus the present study covers case material for the 151 patients being treated with LSD who applied for compensation. The papers, which are kept in the Danish State Archives, comprise: completed application forms; medical records and case notes; in many cases, certificates from psychiatric specialists and, in some cases, comments from relatives, lawyers, other doctors, psychologists, mental health societies, journalists and others; and finally, the semi-structured summaries and conclusions of the tribunal. According to the tribunal papers, a decision on the amount of the compensation was made as all applicants received compensation.

Methods

I was granted access to the LSD case material in the Danish State Archives, having agreed to respect confidentiality under the Archives Law. I carefully reviewed the data twice in 2013. I recorded conventional data such as the name of the hospital, the sex and age of the patients at the year of the treatment, and the social outcome. I also noted the type of information provided to the patient and his/her consent to treatment; however, during the 1960s many of the regulations for new treatment strategies, such as informed consent¹⁰ and ethical considerations, had not yet been introduced into medical practice (Riis, 1976). I also collected information on the number of LSD treatments and the dosages used.

First, I recorded the indication for the LSD treatment as it appeared from the psychiatric diagnosis. At the beginning of the 1960s, all psychiatric departments in Denmark used a list of diagnoses that had been prepared by the Danish Psychiatric Society in 1952. This list was in accordance with the 6th International Classification of Diseases, Revision 6 (*ICD-6*) elaborated by the World Health Organization in 1948 (Strömberg, 1964; WHO, 1949). However, in 1965 the 8th edition (*ICD-8*) gradually took over. At the time of the compensation applications between 1986 and 1988, the *ICD-8* classification of diseases was still in use. In 2013, when I evaluated the data, the *ICD-10* classification had long been the standard diagnostic instrument.

The present study dealt with a patient population that applied in 1986–88 for compensation for psychological and physical harm caused by LSD treatment in the public health care system from 1 January 1960. The following long-term complications were recorded from the case material:

1. Flashback experiences, as defined by the *ICD-10* classification: persistent or 'reliving' of the stressor in intrusive flashbacks, vivid memories, or recurring dreams or in experiencing distress when exposed to circumstances resembling or associated with the stressor (criterion B in category F43.1; WHO, 1993). In the *DSM-IV* (APA, 1994): Hallucinogen persistent perception disorder (flashbacks), category 292.89.
2. Psychotic development, either in the form of schizophrenia or persistent delusional disorder (categories F20 and F22 in the *ICD-10*).
3. Development of persistent or recurrent depression or bipolar disorder (categories F31, F32, F33 and F34 in the *ICD-10*).
4. Development of an anxiety disorder independent of flashback experiences, psychotic development or development of depression (categories fulfilling the criteria for F41.0, F41.1 or 41.9 in the *ICD-10*).
5. Psychosurgery.

Evidence for any of the complications listed above was taken as established if the complication was mentioned either by the applicant and confirmed in one or more of the medical certificates, or just in one or more of the medical certificates. In a few cases, it was evident to me that one or more of the complications were present, even if it was not stated in the case material. I included these cases in my analysis.

For every case, the LSD tribunal wrote a summary and stated the reason for the amount of compensation in the conclusion. The case material on which the tribunal made the decisions was often rather incomplete. For most cases, the tribunal applied for a certificate from a psychiatric specialist. However, in a number of cases this certificate could not be obtained for various reasons, such as the patient refusing to see another psychiatrist. According to the law and the circular, a medical re-examination was not mandatory apart from the short medical certificate on the simple application form. Specialist certificates were obtained in 111 of the 151 patients (74 %) from more than 20 psychiatrists. In the remaining cases, the matter was elucidated by obtaining written responses from the various psychiatric departments and/or obtaining copies of specialist certificates submitted for other purposes, such as an application for disablement pension. In all cases, it was made clear that the LSD tribunal wanted answers to the following questions.

1. What was the patient's psychiatric diagnosis, and what was the patient's mental state before the LSD treatment?
2. What was the patient's mental state immediately after the LSD treatment?
3. What is the patient's actual psychiatric diagnosis, and what is the patient's mental state currently?
4. Considering the patient's mental state before the LSD treatment, what would the prognosis have been at that time?
5. Is the patient's present mental state thus different from this, and in what way?
6. Is it possible or likely that the LSD treatment has influenced the long-term course of the patient's mental state?
7. Is it unlikely that the LSD treatment has influenced the long-term course of the patient's mental state?
8. What has the patient's social course been?

In a minority of the patients, the drug psilocybin was given either alone or in combination with LSD, with similar effects as LSD (Larsen, 2013: 247). In the NHS it was decided that complaints about psilocybin treatment should be handled in the same way as complaints about the LSD treatment.

Results

Hospital and socio-demographic data

The greatest number of LSD treatments took place at Frederiksberg Hospital; treatment also took place throughout Denmark at psychiatric hospitals and departments (see Table 1). LSD treatment was also carried out at two clinics that are not mentioned in Table 1: the University Hospital of Copenhagen, Rigshospitalet (nine patients) and the Montebello Clinic north of Copenhagen (12–14 patients) (Larsen, 2013: 240), but none of these patients applied for compensation.

Figure 1 shows the age and sex distribution of the 151 applicants. The age of the patients at the start of treatment has been defined as the difference between birth year and first treatment year. In a number of cases, the source material does not include the exact date for start of LSD treatment. Many of the female patients especially were very young at the start of treatment. Thus, 25 female patients aged 25 years and younger were treated, compared with 14 male patients in the same age category. Two female patients were less than 18 years of age.

A female patient, 15 years of age in 1962, went through four LSD treatments because of incestuous assaults. Since the assaults, she suffered from frightening hallucinatory-like experiences of crawling reptiles on her body. It was the intention of the responsible consultant psychiatrist to get rid of the frightening experiences through ‘the LSD sessions to realize the unconscious mental life’. However, the condition deteriorated. Later, she suffered from recurrent depression and flashback experiences from the LSD sessions.

A female patient, 17 years of age in 1963, went through three LSD sessions with rather high doses from 200 to 800 micrograms of LSD because of anorexia nervosa. Over the years she was cured of the anorexia nervosa but suffered from mood swings and permanent flashback experiences of the same frightening intensity as during the LSD treatment.

Table 1. Distribution of the 151 LSD treated patients who applied successfully for compensation.

Name of hospital and city	No. applicants	Percentage of total
Frederiksberg Hospital	109	72.2
Oringe, Vordingborg	10	6.6
Sankt Hans Hospital, Roskilde	14	9.3
Augustenborg	2	1.3
The State Hospital of Viborg	2	1.3
Vejle fjord, Vejle	2	1.3
The County and City Hospital of Vejle	2	1.3
Department of Psychiatry, Rønne Hospital	3	2.0
Risskov, Aarhus	4	2.6
Spangsbjerg Hospital, Esbjerg	2	1.3
The Municipal Hospital of Copenhagen	1	0.7
Total	151	

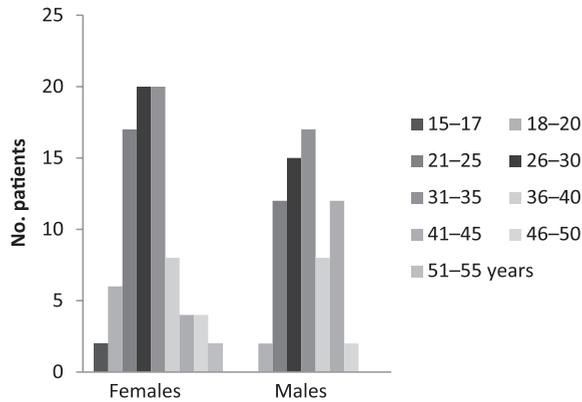


Figure 1. Sex and age distribution of 151 patients (68 males, 83 females) applying for compensation for LSD inflicted harm at the time of LSD treatment.

Table 2. Duration of mental disorder in 151 patients before the beginning of LSD treatment.

Duration (years)	No. patients and percentage (%)
0-1	47 (31%)
1-2	9 (6%)
2-3	18 (12%)
3-5	21 (14%)
5-10	22 (15%)
10-20	20 (13%)
>20	9 (6%)
Not applicable	5 (3%)

No attempt has been made to give a full description of the social status of the patients, either at the time of the LSD treatment or at the time of application for compensation. However, some idea can be obtained by counting the number of patients who were receiving invalidity pension. Of the 151 patients, 91 (60%) were receiving an invalidity pension at the time of application for compensation. In only two cases, the main reason for the pension was a somatic illness; in all other cases, the reason was mental disorder. Roughly half of the remaining patients (20% of the total case material) also had severe social problems, such as inability to work, social isolation and long-lasting sick leave. In eight patients, the invalidity pension was given years before the LSD treatment, for example:

A male patient, 39 years old, later classified as suffering from chronic schizophrenia tried a series of LSD treatments in 1965 as 'a last therapeutic chance'. At that time, he had been sick for more than 20 years and had received an invalidity pension 14 years before the LSD treatment. His condition, however, deteriorated coincident with the LSD treatment and from then on he became a permanent resident in a psychiatric institution.

Table 2 shows the duration of mental disorder before LSD treatment was prescribed. The onset of mental disorder has been defined as the first year of visiting a doctor (i.e., general practitioner, psychiatrist) or, in a few cases, a psychologist for mental health problems.

In 47 of the 151 cases (31%), the LSD treatment was applied within the first year of treatment for the mental disorder, and for 26 of these cases (17%), this was the first treatment choice. Four hospitals used LSD in first year of psychiatric treatment; at Frederiksberg Hospital early LSD-intervention was used for 22 of 109 patients (20%) who, for the most part, suffered from anxiety and depressive disorders.

Type of consent

In 1986 the Danish NHS discussed whether the LSD patients at the time of the treatment in the 1960s were informed according to existing laws and had consented to the treatment as a consequence of this information. Written consent did not exist at that time, and the regulations for informed consent and the introduction of new treatment methods in the form we know today were gradually introduced many years after the LSD treatment took place. The last treatment took place in 1973, three years before the Helsinki-II Declaration established ethical guidelines for medical research with human subjects (Riis, 1976). Thus, the Health Services concluded that sufficient informed consent according to the standards of the past had generally been obtained.¹¹

In the case material, it is possible to count the number of patients who received at least minimal information and who, according to this information, tacitly or openly consented to the LSD treatments. In 65 of the 151 patients (43%), the types of information provided and consent given are not known or registered; three patients needed strong persuasion, and 83 patients (55%) consented according to the information given.

The case material in the State Archives includes examples of the type of information provided:

A 22-year-old man suffered from balbutio. After unsuccessful treatment with hypnotherapy, LSD treatment was suggested to him, to help him remember a long time back, to find the cause of his stuttering. The LSD treatment was described as being without side-effects, which is why the patient followed the advice of the psychiatrist. LSD triggered a depressive illness, and he afterwards suffered from flashbacks. The stuttering remained unchanged.

A 20-year-old man suffered from an anxiety disorder. He went to see the consultant psychiatrist, whom he described as having a 'vigorous hypnotic charisma'. The psychiatrist 'immediately introduced a new treatment, which would render the therapeutic couch and other outdated therapy superfluous'. After three treatments, his condition was described as improved; however, he later suffered from severe anxiety symptoms accompanied by flashbacks.

Number of LSD treatments and dosages

The number of LSD treatments for each patient is shown in Figure 2. The treatment normally started in the morning and was discontinued in the afternoon by giving a benzodiazepine or chlorpromazine. Alternatively, in 7 of the 151 patients (5%), psilocybin was given, either alone or in combination with LSD. Normally, the treatment was administered once or twice a week, often with intervals without LSD treatment. Thus, in a few patients, the treatment continued for years; in other patients, LSD was tested only a few times.

The LSD case material does not systematically include the dosage of LSD given per session, and only 55 (36%) of the cases have some information on the LSD dosages. However, from these patients, the usual dosing can be inferred. In most cases, independently of the diagnosis, the initial dose was rather low, between 25 and 50 micrograms, and the dosage was rapidly increased to a maximum of 200–250 micrograms. In nine of the 55 patients, the starting dose was above 100 micrograms LSD: 150 micrograms (five cases); 200 micrograms (two); 220 micrograms (one); 250

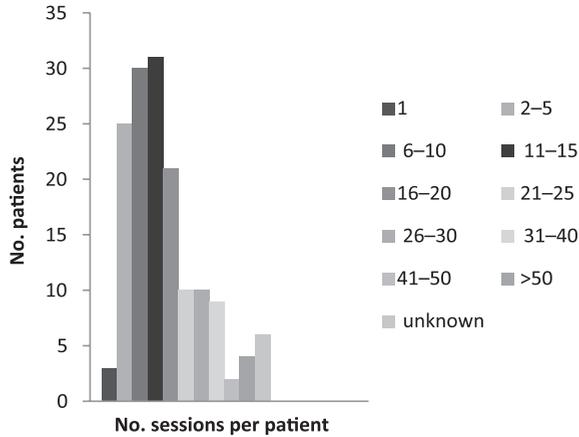


Figure 2. LSD treatment in 151 patients: number of sessions for each patient (seven patients were given psilocybin, either in combination with LSD or alone).

micrograms (one). In 14 cases, the dose was increased to more than 400 micrograms: in one patient, to 700 micrograms, and in three patients, to 800 micrograms. In patients receiving many treatments, the dosage was often kept fairly constant, typically between 100 and 200 micrograms.

Methylphenidate was added in approximately 10% of the cases. The dosages varied from 2 to 10 mg per dosage. Additionally, meprobamate, chlorpromazine, amitriptyline and benzodiazepines were prescribed together with the LSD treatment or used to stop the LSD reaction.

Acute and long-term efficacy of the LSD treatment

In the follow-up study by Geert-Jørgensen et al. (1964) from Frederiksberg Hospital, almost half of the patients had improved and the rest were unchanged. In the early 1960s, the patients had completed a questionnaire, asking, among other things, whether the LSD treatment had helped, had caused harm, or had changed anything and whether the treatment should be recommended to others.

Responses to this questionnaire have been preserved in the LSD case material in a few instances; for example:

A 26-year-old female patient went through 30 LSD treatments. She had suffered for years from depressive neurosis and was found suitable for LSD treatment combined with psychotherapy. On the questionnaire, she responded that LSD had helped quite a lot and, among other things, had made her less inhibited and more outspoken. She would definitely recommend it to others. Because of flashbacks with intense anxiety she was awarded 50% compensation, 125.000 DKK, because she was not considered to have been severely harmed by the LSD treatment and because part of her mental problems existed before the LSD treatment was given.

From my analysis of the case material in the present study, it is also possible to give a rough description of the acute effect of the LSD treatment. Excluding the 17 cases without sufficient information to evaluate the efficacy, results for 134 cases were: 52 (39%) improved, 34 (25%) unchanged, and 48 (36%) worsened. The following examples illustrate the types of clinical effects of the treatment.

A 45-year-old man suffering from mild chronic depression received five LSD treatments of unknown dosage. He responded well to the treatment, and immediately after discontinuation of the treatment, he was less withdrawn and shy. His wife told the doctor that he had become more indiscreet and that his character had changed in an almost alarming way. A few years later, he experienced severe depression and suffered from frightening flashbacks for the rest of his life. He was awarded 50% compensation, 125.000 DKK, because parts of his mental problems were considered to have been present before the LSD-treatment.

A 34-year-old woman received 15 LSD treatments because of anxiety neurosis. The dose was increased to 200 micrograms, and by the fifth treatment, methylphenidate was added. Immediately after the treatments, she experienced increased anxiety; however, she also found the treatment beneficial because she had become less withdrawn. Her private psychiatrist described her as more emancipated and talkative, more forcible and she talked to complete strangers. She was considered to be nearly psychotic, at least extremely tense. After a while she again suffered from the same anxiety symptoms as before the LSD treatment, and she permanently experienced flashbacks, especially at night when falling asleep. She was awarded 60% compensation, 150.000 DKK, because she had succeeded in maintaining a reasonable social function.

Psychiatric diagnosis at the time of LSD treatment compared with diagnosis at the time of the compensation application

LSD was used on a wide spectrum of mental disorders and dysfunctions, as shown in Table 3. The main psychiatric diagnoses in 1986–88 were made by a greater number of general practitioners and psychiatric specialists and were afterwards evaluated, confirmed or, in a few cases, set by the LSD tribunal, when no prior diagnostic information was available. A large number of patients were given a diagnosis within the neurotic categories. In a high percentage of these patients, the case material did not provide information to specify further details of the diagnosis; thus, a diagnosis of depression or of schizophrenia was given only when it was considered to be unlikely that the mental disorder could be classified differently.

Homosexuality was a psychiatric diagnosis until 1981, when it was withdrawn by the Danish NHS, as in other countries. Two patients with homosexuality, according to the psychiatric classification in the 1960s, were unsuccessfully treated with LSD. Additionally, one patient with a gender identity disorder and one patient with sexual dysfunction were treated with LSD. In the latter case a short, but not lasting, improvement was observed.

In 12 cases, it was not possible for the LSD tribunal to determine a psychiatric diagnosis, partly because the cases were administratively handled without obtaining a medical certificate and partly because the certificates and medical case notes were too unreliable.

Short-term and long-term LSD inflicted harm

In the LSD Damages Law, it was anticipated that LSD treatment had been harmful. Thus, in the applications and the certificates, the frightening aspects of the treatment were often brought into focus. The case material provides us with vivid descriptions of the acute LSD experiences and the revival of these in flashbacks: ‘Saw snakes and reptiles; felt that the extremities puffed up and that she was unable to escape’; ‘Saw worms and snakes creeping out of the doctor’s orbits’; ‘The brain is being cut into pieces and is exploding’; ‘Experienced own funeral and that she tried to strangle a nurse’; ‘Dominated by LSD for ever; puffing up of the body at the same time as the urge to take her life was multiplied’; ‘I feel squeezed down into the bed, the face is flattened out by the pressure, then intense experiences of colours moving and accelerating in circles creating a tunnel through which I am sucked under. ...In every session I have used so much energy that

Table 3. The main psychiatric diagnosis at the time of LSD treatment in the 1960s, and at the time of compensation application in 1986–88 (N = 151).

	Diagnosis in 1960s	Diagnosis in 1986–88*
Abuse of alcohol and medicine	2 (1%)	4 (<3%)
Schizophrenia and paranoid psychosis	8 (5%)	21 (14%)
Borderline psychosis	1 (<1%)	8 (5%)
Depression and manic-depressive disorder	17 (11%)	38 (25%)
Depressive neurosis	5 (3%)	0
Character neurosis	53 (35%)	20 (13%)
Anancastic neurosis	19 (<13%)	11 (7%)
Anxiety neurosis	30 (20%)	16 (<11%)
Unspecified neurosis	6 (4%)	9 (6%)
Anorexia nervosa	2 (1%)	0
Personality disorder	2 (1%)	6 (4%)
Sexual dysfunction and gender identity disorders	4 (<3%)	2 (1%)
Gilles de la Tourette's syndrome	0	1 (<1%)
Stuttering	2 (1%)	2 (1%)
Dementia	0	1 (<1%)
Not applicable	0	12 (8%)

*Diagnosis obtained by LSD Tribunal.

it corresponds to the energy of several years'; 'Float away all the time, watching the aura of people and experiencing myself as a skeleton'.

Table 4 summarizes the types of long-term LSD-inflicted harm. Column 2 gives the minimum numbers of patients. A positive rating for flashbacks was given only when they were documented in the medical certificate, the case notes and/or the patient's description. In a few cases, a positive rating for flashbacks was based on the patient's report, and only when I considered it to be certain that the patient had experienced flashbacks.

Symptoms of anxiety occurred in some patients along with flashbacks as part of post-traumatic stress disorder (PTSD) and anxiety disorder diagnoses, as defined according to the *ICD-10* classification. It was not possible to separate these two causes of anxiety as they were often overlapping.

As in the group of psychotic and schizophrenic patients, the number of patients being treated with LSD because of depression or bipolar disorder was also recorded. In fact, no patients were diagnosed with bipolar disorder prior to the LSD treatment. However, it later seemed probable that at least two LSD patients suffered from bipolar disorder prior to treatment. Eight patients underwent psychosurgery. LSD treatment was typically carried out as a last choice before the surgical intervention. In those patients, the LSD treatment mostly worsened the patient's mental state; however, the psychosurgical intervention caused some improvement, although the patients were still severely ill.

A 34-year-old female patient was given 22 LSD treatments starting with 50 micrograms and ending with 300 micrograms per session. Two years before, she had been admitted to a psychiatric department because of anxiety and depression after giving birth. She recovered and was then re-admitted after her second birth with symptoms of depression and anxiety, including homicidal impulses against her two children. She partly recovered after ECT treatment and was offered LSD treatment as an outpatient. During the LSD sessions, she experienced increased anxiety and was recommended to have a psychosurgical intervention,

Table 4. Long-term LSD inflicted harm at follow-up (1986–88) in 151 patients.

	No. patients	Percentage
Psychosurgical intervention	8	5
Further development of schizophrenia or delusional disorder	21	14
Further development of bipolar disorder or depressive disorder	38	25
Further development of anxiety disorder or experience of anxiety together with flashbacks	100–120	66–79
Flashbacks	104	69
None	5	<4

which she accepted. Consequently, she was given ... a cingulectomy. Some of the anxiety disappeared; however, she was later admitted for endogenous depression multiple times. She received a disablement pension and permanently suffered from flashbacks, anxiety and sleep disturbances. She was awarded with the maximum compensation, 255.000 DKK (100 %), and later received another 75.000 DKK.

The financial compensation for the LSD inflicted harm

In each successful case, the LSD Tribunal made a summary and a conclusion from which the amount of compensation was decided. According to the circular from the NHS, the amount was determined by the extent of the damages (Larsen, 2013: 256). Examples of compensation awarded are included in some of the cases quoted above. Reasons for a lower compensation figure included: reasonably good social functioning after the treatment; severe and long-lasting mental illness before the treatment; and few LSD treatments. On the other hand, patients who underwent psychosurgery or became severely psychotic were often awarded higher compensation. The amount of compensation ranged from 50.000 to 510.000 DKK (Larsen, 2013: 257).

Under the Law, 12 of the patients who applied for compensation were awarded free treatment. It has not been possible, however, to assess the cost of this.

Discussion

Although LSD was used in psychiatry at many clinics in the USA and Europe in the 1950s and 1960s, very few long-term follow-up studies have been done. Generally the results of the treatment were considered to be promising (Leuner and Holfield, 1962; Sandison and Whitelaw, 1957). However, early warnings (Frosch, Robbins and Stern, 1962; Grinker, 1963; Rinkel, 1966) and a wave of illegal use resulted in restrictions for its medical use and, soon after, withdrawal from the market (Larsen, 2013: 229; Ungerleider, 1968). Despite these facts, LSD remained an interesting tool in psychotherapeutic circles, as demonstrated in many papers read and discussed at the Second International Conference on the Use of LSD in Psychotherapy and Alcoholism in New York, May 1965. None of the papers discussed possible acute or long-term side-effects, nor adequately challenged the contemporary criticism of the use of LSD in psychiatry (Abramson, 1967: 577).

Interestingly, in Denmark and Norway, medical use of LSD continued until the mid-1970s, approximately 10 years after the treatment became internationally contentious, and then was gradually discontinued (Due-Madsen and Hoffart, 1996; Larsen, 2013: 260). In a 1964 Danish follow-up study, only a few complications were found (Geert-Jørgensen et al., 1964: 375). Similar results were found in Norway in the first three years of LSD treatment (Johnsen, 1964), and also in a follow-up study in 1967, which was completed nearly 20 years later (Due-Madsen et al., 1996).

The above results were strikingly different from the findings of the present study, which describes the overall mental state in a population of psychiatric patients approximately 25 years after they were treated with LSD. It found that 36% of the patients deteriorated simultaneously with the LSD treatment and that nearly all the patients suffered from long-term side-effects. There may be many explanations for these discrepancies.

First, the patient sample in the present study was restricted to patients complaining of harm due to LSD treatment. These 151 patients represent less than 40% of the total of 400 patients treated with LSD, because case notes and medical records of the remaining patients have not been preserved. Thus, it cannot be proved that only patients suffering from the LSD treatment applied for compensation. However, this argument is unlikely, as the LSD Damages Law included reversed burden of evidence, meaning that any patient being treated with LSD and applying for compensation would receive an award (LSD Damages Law, 1986).

Another point that is often made concerns the lack of psychotherapy with the LSD treatment at Frederiksberg Hospital compared with other clinics in Denmark. However, patients being treated with LSD at clinics with strong psychoanalytical approaches also deteriorated and suffered from severe side-effects. Nevertheless, no application for compensation came from any of the 21–23 patients being treated with LSD at two psychoanalytic clinics in the Copenhagen area.¹² In the present study it was not possible to analyse why some patients applied for compensation and others did not, because of insufficient information.

Second, LSD may have cured or greatly improved the mental disorder only in patients with minor mental problems and in certain patient populations, which is why they did not apply for compensation. Both suggestions are considered to be unlikely. In the present study, LSD treatment did not cure stuttering in two patients, but instead resulted in long-lasting side-effects in both cases. Moreover, deterioration of the mental state was observed independently of the diagnosis, even in patients with obsessive-compulsive disorder. Obsessional neurosis was one of the suggested indications when LSD was introduced into clinical use, and it became the preferred indication in the later years of LSD treatment (Brandrup and Vanggaard, 1977; Hofmann, 1980: 31). To analyse the outcome of LSD treatment across the diagnostic spectrum, we would need data from follow-up studies of sufficient duration and with a critical analysis of possible bias. However, such studies do not exist.

Third, the number of patients with LSD inflicted problems found 25 years after the treatment, such as further development of schizophrenia, delusional disorder, or affective disorder, may reflect the natural course of these disorders, independently of the treatment. This can only be partly denied. However, the unexpectedly high occurrence of flashbacks accompanied by anxiety is not normally observed in a population of patients with mental disorders who were not otherwise traumatized. The LSD treatment undoubtedly caused these results.

At the time of LSD treatment, flashbacks were considered to be rare side-effects (Geert-Jørgensen et al., 1964: 375; Leuner, 1968: 114–16). Side-effects were not considered in the 1964 Norwegian follow-up study (Due-Madsen et al., 1996), and were not observed in many international studies (Abramson, 1967). This was most likely because side-effects were under-reported; in fact, contemporary LSD researchers were aware of their existence:

One of the most frequently reported chronic side effects from LSD is the recurrence of a portion of the original LSD experience without using the drug again ... The LSD experience seemed to be precipitated by stress ... we have seen cases in which there seemed to be no apparent stress. (Fisher, 1968: 69–71)

However, the present study demonstrates that flashbacks and anxiety symptoms alone or in combination were the rule rather than the exception. Flashbacks were not well understood at that time.

In a study from 1976, it was suggested that they were conversion reactions (Saidel and Babineau, 1976). However, the reappearance of LSD symptoms in three patients after they had stopped taking LSD made hospitalization necessary; the intensity and number of symptoms were related to the number of LSD exposures and severe psychopathology (schizophrenia) (Frosch et al., 1962). On the other hand, Bernstein (1988: 508) was not able to predict who would experience a 'bad trip' or flashbacks. A study on the benefits following LSD in 74 alcoholics did not mention flashbacks or side-effects at all (Ditman, Hayman and Whittlesbey, 1962).

In some of the early studies, it was considered that flashback experiences were not caused by psychedelic drugs as a true drug effect (Heaton, 1975); however, later reviews undoubtedly accepted the potential of LSD to create flashbacks (Halpern and Pope, 2003; Strassman 1984). Halpern and Pope (2003: 115) found that flashbacks (hallucinogen persisting perception disorder), as defined in the *DSM-IV* (APA, 1994), were most commonly reported with illicit LSD use and less commonly with LSD administered in research or treatment settings. Also Strassman (1984: 591), in his review of the literature, was inclined to think that flashbacks were associated with existing psychopathology and associated drug use. However, he reported that flashbacks with psychedelic drugs were found at an incidence of approximately 50 per cent.

In the study of a group of alcoholics by Ditman et al. (1962), a very high percentage of the patients claimed improvement in the first six months after LSD treatment; however, three-and-a-half years later, they claimed only slight improvement and none of them maintained their sobriety. It was hypothesized that LSD may have a direct chemical influence on areas of the brain, producing a sustained euphoria or altered mood, like some of the newer antidepressants (Ditman et al., 1962: 351).

Reports of an acute therapeutic effect on a variety of mental disorders were most likely the driving force in the early enthusiasm for LSD therapy. The modern era of psychopharmacology had not yet had its breakthrough, and psycholytic therapy with LSD was seen to be a (happy) marriage of psychoanalysis and psychopharmaceutics (Snelders and Kaplan, 2002: 229). According to Dyck (2005), the withdrawal of LSD in the 1960s had as well to do with the state-of-the-art of scientific research. From the early 1960s, the scientific paradigm of clinical trials shifted to necessitate randomized clinical trials, which were never conducted with LSD treatment. A similar point of view was recently expressed by Oram (2014), who found that the emphasis on controlled clinical trials frustrated the progress of LSD psychotherapy research and consequently led to the death of LSD treatment.

Furthermore, the discrepancy between the findings in the 1964 Danish follow-up study (Geert-Jørgensen et al., 1964) and the present study may be partly explained by the acute stimulating effects of LSD. For years, it has been known that LSD, with a structural similarity to indolamines such as serotonin, exerts agonistic effects at presynaptic serotonin receptors (Bernstein, 1988: 507). The mechanisms of action on brain receptors are still not fully understood. Although LSD is a partial agonist of the 5-HT_{2A} receptor (i.e. the hallucinogen receptor), it also has agonistic effects on 5-HT_{1A} receptors and interacts agonistically and antagonistically with dopamine D₁ and D₂ receptors (Baumeister, Barnes, Giaroli and Tracy, 2014; Passie, Halpern, Stichtenoth, Emrich and Hintzen, 2008).

Considering the early enthusiasm for LSD treatment, it is not surprising that it has again created interest. Recent studies have suggested that LSD treatment is safe and effective when assisting psychotherapy for anxiety associated with life-threatening diseases (Gasser et al., 2014), and that the hallucinogens may be used as antidepressants, bearing in mind the acute stimulating effect on serotonin receptors (Baumeister et al., 2014). Targets for LSD therapy include illnesses that are difficult to treat, such as end-of-life anxiety in the terminally ill, PTSD, cancer, addiction and cluster headaches (Passie et al., 2008; Smith, Raswyck and Davidson, 2014).

In the light of the findings of the present study, the prospects of clinical use seem frightening. We know little about the long-term effects. We have some idea of the acute stimulating effects, but, depending on dose and number of treatments, there is a substantial risk of long-term side-effects. LSD, with its obvious neurotoxic qualities, may be better tolerated by individuals without severe psychopathology, as suggested by Cohen (1960: 35–6). The present study has demonstrated that the condition of the majority of the patients, most of them severely mentally ill, worsened. A possible clinical use should focus on selection criteria before treatment; again we have little knowledge in this field, and reading the many papers on LSD therapy from the past does not provide much help. At that time, the principal interest was more the results of the LSD treatment than sorting out the responders from the non-responders using clinical criteria. Moreover, nearly all the studies missed the opportunity to recognize the acute effects of LSD as unwanted. It might have been more fruitful to have followed a strategy that took brain science into consideration, as later suggested by Skinner (1990: 1206): ‘where processes may be said to be inspected rather than introspected’.

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Declaration of interests

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Notes

1. This and other quotations have been translated by the present author.
2. The Danish psychiatrist Thorkil Vanggaard (1910–98) strongly advocated that psychoanalytic therapy and LSD therapy were alternative strategies, as LSD suspended ‘repression’ and gave insight into the unconscious.
3. In 1968 a questionnaire was sent to the 300 patients being treated from 1961 to 1967. These questionnaires were analysed nearly 20 years later. There are no scientific data on the course of events since 1968.
4. According to unpublished data belonging to the author.
5. Sundhedsstyrelsen: Redegørelse for LSD-sagens Forløb. Rigsarkivet. [NHS: Account of the course of the LSD case]. Danish State Archives, IM. I. s. kt., j.nr.5740/0-1985.
6. All clinical illustrations and details of the case histories are taken from the individual case records kept in the Danish State Archives.
7. See Note 5.
8. The medico-legal counsel wrote on 11 December 1975 that at that time (1961–65), no information existed to suggest that it could be dangerous to use LSD for practically all psychiatric conditions, including the case of this patient. This statement was again quoted in 1988 at the patient’s trial against the medico-legal counsel.
9. The Danish text says: ‘For skade, som er eller kan være forårsaget af behandlingen med LSD, anses behandlingen for at være årsagen, med mindre det er overvejende sandsynligt, at skaden har anden årsag.’
10. ‘Circular of informed consent’. The National Health Service of Denmark, 21 October 1982 (in Danish).

11. See Note 5.
12. At the Montebello Clinic (12–14 patients), the results were not considered to be unequivocal (Larsen, 2013: 240), and at Rigshospitalet, five of the nine patients improved and four were unchanged. The latter information appears in an enclosure to the ‘Account of the course of the LSD-case’ (see Note 5).

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