

Early LSD treatment in Denmark from 1960 to 1974

An analysis of possible and long-lasting changes in the adult personality following psychedelic treatment. A historical retrospective cohort study

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Abstract

In view of the renewed interest in psychedelics in psychiatry it is timely to analyze psychedelic treatment in historical cohorts. Recently the therapeutic efficacy of psychedelics has been linked to the so-called phenomenon of “connectedness.” The aim of the present study was to explore whether long-lasting personality changes were observed in any of the 151 Danish psychiatric patients who were treated with Lysergic acid diethylamide (LSD) from 1960 to 1974.

The exploration included a reanalysis of a subgroup as well from a 1964 Danish historical cohort. Medical records and other case materials of the above mentioned 151 patients are kept in the Danish State Archives. The present author was granted access to the LSD case materials in the Danish State Archives, and respected confidentiality per the Archives Law. According to the LSD Damages Law from 1986, they all received financial compensation for LSD-inflicted harm.

Analysis did not reveal any personality changes such as “connectedness;” however, other lasting personality changes were observed in 2 to 4 patients and in quite a few patients unwanted effects persisted for weeks or months following acute treatment. In the present analysis of the 1964 cohort, the same percentage of patients improved with LSD treatment as in the historical analysis. In the latter, however, little attention was given to side effects, such as suicide attempts, suicides, and one homicide.

Future psychedelic research with psychiatric patients should respect the potential toxicity of LSD and other psychedelics and meticulously monitor possible side effects.

Abbreviation: LSD = lysergic acid diethylamide.

Keywords: long-term treatment outcome, lysergic acid diethylamide, personality change, psychedelic treatment, short-term treatment outcome

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]; The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

1.1. Psychedelic treatment: The state of the art

In an editorial, David Nutt wrote, “It’s time to take psychedelic treatments in psychiatry . . . seriously, as we did in the 1950s and 1960s.”^[1, p. 1163] The early experiences, however, also included warnings in other journal editorials, emphasizing the increased risk of psychosis and suicide with psychedelic treatment.^[2,3] Furthermore, concerns about the clinical use of Lysergic acid diethylamide (LSD) and psilocybin were advanced in a follow-up study of 151 Danish patients, approximately 25 years after they received treatment in the 1960s.^[4,5] The original paper on LSD therapy in Denmark is also worth mentioning. Although predominantly positive conclusions about its potential were claimed throughout its use from 1960 to 1974,^[6] by 1964, one homicide, two completed suicides, and four suicide attempts had been reported in the 129-patient cohort.^[7]

1.2. Psychedelic treatment: mechanisms of action

Compared to the 1960s, we are much better prepared today to explain the mechanisms underlying the action of LSD and other psychedelics. As summarized elsewhere, 5-hydroxy tryptamine 2 receptors are major targets for a wide array of psychoactive drugs, including psychedelics such as LSD and psilocybin.^[8,9]

Psychedelics alter the functioning of the serotonergic system, but not in the same manner as current antidepressants.^[9] With classical antidepressants, delayed recovery commonly begins three weeks after starting the medication.^[10] This phenomenon has been explained as being due to the autoregulation of serotonin receptors.^[11] With psychedelics, the therapeutic response starts after a few hours, when the hallucinogenic effect has worn off.^[8]

1.3. Psychedelic treatment: connectedness

The therapeutic efficacy of psychedelics has been linked to the so-called phenomenon of “connectedness,” which has been proposed as the key to understanding how psychedelics work.^[12] Thus, in order to identify patients’ experiences of psilocybin treatment, 20 patients with treatment-resistant depression participated in a semi-structured interview at six-months follow-up. Two major themes of the treatment benefits were identified:

- (1) a change from disconnection (from self, others, and the outside world) to connection, and
- (2) a change from avoidance of difficult emotions and memories to acceptance.^[13]

However, subjective claims of long-term changes in adult personality after LSD treatment were already reported in uncontrolled trials from the 1960s.^[14–17] However, in those early studies, such claims were found to be controversial, subtle, and nonsignificant,^[16] as little evidence for lasting changes in personality was found.^[15] In the modern era of psychedelic research, mystical experiences and personality changes were observed in healthy adults more than one year after administration of a high dose (30 mg/70 kg) of psilocybin.^[18]

1.4. LSD treatment: antidepressant effect, change in personality, harm

Thus, the possible beneficial effects of psychedelic treatment have been recorded, as well as a symptomatic effect (e.g., antidepressant) as a qualitative effect on underlying personality traits.^[19] In detail, these aspects have been reported in a case study. A 30-year-old man with an incapacitating compulsive neurosis took part in 57 LSD sessions from October 1962 to January 1964. After the first three sessions, he received 100 µg of LSD each time. While under the influence of the drug, he was left alone; however, between sessions, he reported his experiences during the sessions to the doctor. Strikingly, the reports indicated not only the disappearance of his neurotic symptoms (symptomatic effect) but also a significant change in his overall personality (qualitative effect), “particularly concerning the emotional part of it. He became a much warmer person, with easily mobilized emotions, and the rigidity of his trend of thought gave way to freely varied thinking, a mobilization of his fantasy life, and a more humorous approach to life.”^{[20][20, p. 139]}

In Danish follow-up studies on short- and long-term treatment outcomes, mainly data on symptomatic effects and harm have been presented.^[4,5] These studies did not consider that long-lasting treatment effects of single sessions with psychedelic-assisted therapy might be obtained, or that “these enduring effects are suggestive of a paradigm very different in nature from conventional pharmacological treatments.”^{[21][21 p. 487]}

1.5. Aims

The present study aimed to explore whether long-lasting personality changes were observed in any of the 151 Danish psychiatric patients who were treated with LSD from 1960 to 1974, as well as to assess whether such possible changes in adult personality might suggest a quality of connectedness. Short- and long-term treatment outcomes for these individuals were also assessed. Analyses were conducted with a subgroup of 54 patients identified from the 1964 LSD treatment cohort.

2. Methods

2.1. Patients

In Denmark, from 1959 to 1973, nearly 400 patients were treated with LSD. Medical records and other case materials of 151 patients who were treated with LSD and reported these treatments caused them harm are kept in the Danish State Archives. All 151 patients treated with LSD (LSD case materials) received financial compensation, according to the LSD Damages Law of 1986.^[22] Regarding the law, a “reversed burden of proof” was described as follows: “For harm, which is caused by or may be caused by treatment with LSD, this treatment is regarded to be the cause (of the harm), unless it is likely that the harm is due to another cause” (LSD Damages Law, 1986). Each application was handled by a tribunal under the Ministry of Social Affairs (the LSD tribunal).

The present author was granted access to the LSD case materials in the Danish State Archives, and respected confidentiality per the Archives Law. All LSD case materials were carefully reviewed twice, first from winter to spring 2013 and then in autumn 2013. Detailed descriptions of the basis for the LSD tribunal’s verdicts and short- and long-term treatment outcomes of the LSD treatment have been published elsewhere.^[4–6]

2.2. Sessions and dosage

LSD and/or psilocybin was administered once or twice a week, often interspaced with periods of weeks or months without treatment. The initial dose of LSD was, in most cases, 25 or 50 µg, and the dosage was rapidly increased to 200 to 250 µg, or even higher for a few patients. If data were available, the LSD dose-index (number of treatments multiplied by the maximal LSD dose and divided by 100) was calculated.^[5] The doses of psilocybin in 11 patients were between 8 mg and 32 mg.

During the treatment at Frederiksberg Hospital, where most of the treatments took place, patients were left alone in a quiet room, with a nurse available in case of an emergency. The nurse sat outside the closed door of the treatment room. The patients either consulted the prescribing doctor the day after the session or between sessions. No systematic psychotherapy was implemented; however, the doctor’s attitude toward the patients was eventually described as supportive.^[23,24] As published elsewhere, except for three patients who required strong persuasion, most patients, for whom data are available, consented openly or tacitly to the treatment.^[4] Additionally, the treatment was not administered under coercion, as it has recently been advanced.^[25] Until 1964, most patients at Frederiksberg Hospital received outpatient treatment; however, following a homicide, patients then stayed overnight at the hospital after receiving LSD.

2.3. Measures and diagnosis

Of the first 132 patients treated at Frederiksberg Hospital until June 1964, the treatment outcomes for 129 of these patients were estimated to be either improved or unchanged, as none of the patients in the original paper published in 1964 showed signs of a deteriorated condition.^[7] Thus, the occurrences of one homicide, two completed suicides, and four suicide attempts were not found to be inconsistent with the estimation of improved or unchanged mental states. The measures used in the 1964 study were based on questionnaires, filled out by the patients. Three patients did not participate in the follow-up evaluation and were thus excluded from the study. Unfortunately, these questionnaires have not been preserved, except for that of one patient. The total number of patients commencing LSD treatment before June 1964 included another 28 patients, who were also excluded from the follow-up study because they did not complete the treatment.^[7] However, the LSD case materials allow for the identification of a subgroup of patients treated with LSD at Frederiksberg Hospital until June 1964, and data of the short- and long-term outcome in this subgroup is presented in the Results section.

The LSD tribunal made inquiries regarding patients' former and present mental states. Of course, the phenomenon of "connectedness" was not assessed, as this phenomenon was not defined until many years later.^[12] However, the increased attention on one's mental state after receiving LSD treatment makes it possible to determine whether a state such as connectedness or any other personality changes were present.

The LSD tribunal established diagnoses in accordance with the International Classification of Diseases in use at that time, as defined by the World Health Organization (WHO). The sixth edition (ICD-6) was used at the start of LSD treatment; however, starting in 1965, a transition was made to the eighth edition.^[26,27]

2.4. Ethical review

Approval from ethical committees is not required in this type of research in Denmark. However, a confidentiality agreement must be signed. Access to the LSD case materials was approved by agreeing to respect confidentiality under the (Danish) Archives Law.

3. Results

3.1. Frederiksberg subgroup of patients treated with LSD from 1960 to June 1964

The LSD case materials included a subgroup of 54 patients, who were treated with psychedelics before June 1964 at Frederiksberg Hospital. Out of a total group of 129 patients, all these 54 patients (42%) were only treated with LSD, as use of psilocybin was introduced in the later years of psychedelic treatment in Denmark. Several patients also received methylphenidate. Personally, identifiable data were not preserved and, accordingly, such information from the LSD case materials (151 patients) is not presented here. It was also not possible to determine if the three patients who were not included in the 1964 evaluation, or the 28 patients who did not complete the treatment and were excluded,^[7] either applied or did not apply for compensation, according to the LSD Damages Law.^[22] Specifically, answers to the following three questions were searched for by the LSD tribunal:

- (1) What were the patient's psychiatric diagnoses, and what was the patient's mental state before LSD treatment;
- (2) What was the patient's mental state immediately after LSD treatment; and
- (3) What is the patient's actual psychiatric diagnosis, and what is the patient's current mental state?

Table 1 shows the acute effects, long-term effects, and diagnoses obtained by the LSD tribunal in these 54 out of the 129 (42%) patients treated early at Frederiksberg Hospital, who represent 54 of the total 151 (36%) patients with LSD case materials, and 54 of the 109 (50%) patients with LSD case materials from Frederiksberg Hospital.^[4] Acute effects were evaluated as improved, unchanged, or deteriorated. In Table 4 of the 1964 paper, a similar description of the outcomes was performed, although at that time, none of patients were classified as having a deteriorated condition. Likewise, the diagnoses obtained by the LSD tribunal were slightly different than those obtained in 1964. In the 1964 cohort, 59 patients were found to have improved and 70 patients were unchanged.^[7] The 1986 evaluation found significantly fewer patients unchanged than the 1964 evaluation (Fisher exact test, $P < .01$) and the condition of

Table 1
The 1986 evaluation. Short- and long-term outcomes of 54 psychiatric patients treated with LSD at Frederiksberg Hospital until June 1964*.

Diagnosis	Short-term outcome					Long-term outcome		
	N	I (n)	U (n)	D (n)	NA	P (n)	D (n)	FB (n)
Anankastic neurosis	4	0	1	2	1	2		1
Anxiety neurosis	5	3	1	1		1		4
† Character neurosis	26	10	3	6	7	4	4	18
Depressive neurosis	2	2	0	0				1
Sexual neurosis	3	2	1	0			2	3
Mental depression	10	5	2	3		2	1	10
Schizo-phrenia	1	0	0	1		1		1
Paranoid syndrome	3	3					1	1
Total	54	25/54	8/54	13/54	8/54	10/54	8/54	39/54
%	100	46	15	24	15	19	15	72

D = deteriorated, D = development of depression, FB = flashbacks, I = improved, NA = not applicable., P = psychotic development, U = unchanged.

* Diagnosed by the 6th edition of the International Classification of Diseases, established by the LSD tribunal (1986-1988).

† 1 patient with personality disorder, 1 patient with hypochondriac neurosis.

14 of the 54 (24%) patients had deteriorated, compared to none in 1964.

3.2. Changes in personality

As shown in Table 2, accounts on personality changes following LSD or psilocybin treatment have been recorded for 38 patients, from patients' reflections, doctors' observations, or comments from relatives. For the 38 patients presented in Table 2, enough information to calculate the LSD dose-index was available for 22 of 36 (61%), as 2 patients were treated with psilocybin. In these 22 patients, the median LSD dose-index was 28 (range 1.5–376). Only for one patient, Number 7 (number not identical to the

index number of the LSD case materials), has the questionnaire from the May 1964 follow-up been preserved. The patient answered that the treatment did not help, it was unpleasant, she would not recommend it to others, it did not harm her, and she did not become more disinhibited, although she did feel deeply attached to the doctor.

Apart from two patients (cases numbers 22 and 36), and possibly another two patients (cases numbers 12 and 19), describing personality changes, no typical pattern was found in the remaining patients. Some patients became more disinhibited, others suffered from mood swings, and some complained about memory disturbances. Hardly any unconditional positive outcomes were reported or observed.

Table 2
Accounts of possible personality changes after LSD or psilocybin treatment in 38/151 patients^{*}

Primary ICD-6 or ICD-8 psychiatric diagnosis	Account of personality change	Long-term unwanted effect (1986–1988)	LSD dose-effect index [†] /N [‡] /max dose (μg)
1 Depressive neurosis	Mortal dread, split mind, changed	Flashbacks, depression [§]	11,2/14/80
2 Depression	She becomes sexually aroused when she watches men's trousers	Flashbacks, psychosis [¶]	–/6/–
3 Anorexia nervosa	Mood swings	Flashbacks	24/3/800
4 Personality disorder	Alternately crying and being euphorically silly	Flashbacks, depression [§]	148,5/27/550
5 Anankastic neurosis	Crying and screaming with self-hatred	Flashbacks	–/9/–
6 Anxiety neurosis	Impaired defense mechanisms	Flashbacks	–/12/–
7 Depression	Denies any emotional change, but deeply attached to the doctor	Flashbacks, psychosis [¶]	–/–/–
8 Anxiety neurosis	Realizes own aggressive inclinations	Flashbacks	26/65/250
9 Depression	Impulsivity, uncontrolled behavior	Flashbacks	2,5/5/50
10 Anxiety neurosis	Unable to separate reality from fantasy	Flashbacks	–/20/–
11 Paranoid psychosis	Released uncontrollable strengths	Psychosis [¶]	7,5/3/250
12 Character neurosis	LSD made him more “soft-minded”	Flashbacks	–/7/–
13 Anxiety neurosis	More likely to act on impulse	Depression [§]	–/3/–
14 Depressive neurosis	Like brainwashing, more outspoken	Flashbacks	–/30/–
15 Stuttering	Afraid of impulsive-ness, did not dare to handle firearms	Flashbacks	13/13/100
16 Anxiety neurosis	Temporary success, though horrifying	Flashbacks	–/18/–
17 Anxiety neurosis	More outspoken, boundless thoughts, scary changes	Flashbacks	–/5/–
18 Character neurosis	Outbursts of weeping	Flashbacks	24/30/80
19 Character neurosis	Deteriorated memory, “dried-up”	Flashbacks	–/6/–
20 Character neurosis	Never escaped from LSD intoxication		96/32/300
21 Depressive neurosis	Momentarily unstable, smashed a TV	Flashbacks	37,5/15/250
22 Depression	Colleagues did not recognize him	Flashbacks	–/3/–
23 Character neurosis	Terrified due to experience of own death	Flashbacks	136,5/21/650
24 Character neurosis	Became overexcited (“hypomania”?)	Depression [§]	1,5/1/150
25 Character neurosis	Though deteriorated, regretful of early termination of LSD-treatment	Flashbacks	–/36/–
26 Anxiety neurosis	Looser in way of thinking	Flashbacks	14/14/10
27 Sexual neurosis	Developed constant nervousness after LSD applied to treat homosexuality	Flashbacks, depression [§]	60/30/200
28 Personality disorder	Feels like a much older man than corresponds to chronological age	Flashbacks	376/47/800
29 Schizophrenia	Sexually aroused during LSD-treatment	Flashbacks, psychosis [¶]	51/17/300
30 Unspecified neurosis	No longer able to solve mathematical problems	Flashbacks	–/32/–
31 Depressive neurosis	After LSD-treatment, considered to be an almost insane person	Flashbacks, depression [§]	70/14/500
32 Depression	“Went to pieces” after psilocybin treatment	Psychosis [¶]	17 weekly sessions, 6–24 mg
33 Anxiety neurosis	More frank, almost silly after psilocybin treatment	Psychosis [¶]	16 weekly sessions, 4–32 mg
34 Anxiety neurosis	More talkative, gets talking with complete strangers	Flashbacks	30/15/200
35 Depression	Positive response to LSD-treatment, which was considered to be as well pleasant as unpleasant	Flashbacks	51,3/19/270
36 Unspecified neurosis	Wife considered her husband not to be the same person as before LSD-treatment		62,1/23/270
37 Anxiety neurosis	Felt in excellent spirits one week after end of LSD-treatment		12/12/100
38 Anxiety neurosis	More unbalanced after LSD-treatment	Psychosurgical intervention	8,75/7/125

^{*} Diagnosis per the 6th (ICD-6) or 8th (ICD-8) editions of the international Classifications of Diseases at the time of the psychedelic treatment, 1960–1974.

[†] LSD dose effect index: Maximal LSD dose multiplied by the number of sessions, divided by 100.

[‡] N: Number of sessions.

[§] Further development of bipolar disorder or depressive disorder.

[¶] Further development of schizophrenia or delusional disorder.

Fourteen of the 38 (37%) patients in Table 2 were included in the Frederiksberg subgroup of patients treated with LSD (Table 1). A closer analysis of the personality changes in this subgroup did not reveal any differences in personality changes, compared with the remaining 24 patients in Table 2. It is worthwhile to mention that within a group of 14 patients (case numbers 4, 7, 9, 12, 14, 18, 22, 24, 27, 29, 30, 34, 35, and 36; numbers not identical to the index numbers of the LSD case material), 10 patients (case numbers 7, 9, 12, 14, 18, 27, 30, 34, 35, and 36; 71%) were reported to show improved or unchanged acute effects. However, in case number 22 with a remarkable personality change, as a deteriorated condition was found at the acute follow-up.

4. Discussion

First, it is important to highlight that the present study deals with patients treated with LSD and possible changes in adult personality that can occur with this treatment. Psychedelic treatment with psilocybin, either alone or as an add-on, was only conducted with a few patients (two patients in Table 2). Modern psychedelic treatment is more closely related to psilocybin, not to LSD. It is, however, generally accepted that the possible side effects, mechanisms of action, and psychedelic potentials are similar for the two drugs. This identity was accepted by the Danish National Health Service in 1985.^[4,28] Also, the present time's researchers in psychedelic therapy equals the potential clinical actions of psilocybin and LSD.^[21,29]

Second, no personally identifiable data (except for one patient) exist for the 129 patients of the 1964 Danish historical cohort. Therefore, it is technically possible that the historical cohort does not include all 54 patients who were treated with LSD at Frederiksberg Hospital before June 1964. Some of the 31 excluded patients from the 1964 study may have applied for compensation as well. Thus, the two populations are not directly comparable in all aspects.

4.1. Psychedelic treatment: mechanisms of action

The early enthusiasm for the use of psychedelics in psychiatry was, to a great extent, focused on their potential ability to speed up psychoanalysis.^[19,30,31] Psychoanalysis and psychoanalytical therapy intend to create a change of a patient's mental state by insight into unconscious processes. LSD was believed to evoke such unconscious processes or material, the analysis of which through interpretation was believed to have curative potential.^[32,33] Along the same lines was the idea that LSD by itself worked on one's unconscious, thus eliminating defense mechanisms. Therefore, psychedelic therapy and psychoanalytical therapy were understood as alternative strategies;^[20,34] however, both strategies focused on the evoked psychedelic experiences.

At that time, little attention was given to the stimulating potential on brain receptors. Today, we know that the action mechanisms of psychedelics are linked to the serotonin system, especially the 5HT2 receptor family.^[8,9] For the present author, it is easy to understand the stimulating potential as the real curative potential, and the hallucinatory experiences as unwanted effects or signs of intoxication. Unwanted effects in the sense of long-term experiences of hallucinatory states during LSD treatments, such as flashbacks, were recorded in the majority of the 151 psychiatric patients, in a follow-up study.^[4] A detailed analysis of the short- and long-term treatment outcomes of those 151

patients has been published elsewhere.^[4,5] It was concluded that, "the use of LSD and psilocybin in mental health patients may be associated with serious short- and long-term side effects."^[5 p. 489]

Recently the association between psychedelics and the generation of "mystical experiences" has been proposed as a key to understanding or predicting well-being after psychedelic therapy.^[18] The analyses included 52 hallucinogen-naïve participants (healthy adults), who completed 2 to 5, 8-hour sessions with psilocybin (30 mg/70 kg body weight). Among others, measures included the NEO Personality Inventory and the Mysticism Scale.^[18] Significant increases in the domain of "Openness" on the NEO Personality Inventory were found; furthermore, this "Openness" remained significantly higher than baseline more than one year after the session in participants who reported mystical experiences during their psilocybin sessions.^[18] The early LSD treatment did not focus on possible changes in underlying personality if such changes appeared. Possible changes in adult personality were, however, documented in an early Danish case study,^[20] and in 2 to 4 patients in the present paper (Table 2). In the latter, these changes were not desirable, and possibly also unforeseen, as they generally had little connection with the mental disorder being treated through the use of psychedelics. In one example from Table 2, case number 22, the man's colleagues did not recognize this middle-aged man after he was treated for depression with LSD; he was like a stranger to them. Although Maclean et al.^[18 p. 1459] "did not directly investigate the corollary benefits of increased openness . . ." in a mental health population, but in healthy adults, they nevertheless suggested that hallucinogens could have positive effects on mental health outcomes, particularly for anxiety and mood disorders.^[18]

4.2. Psychedelic treatment: psychotic development

Since the late 1960s, it has been well-known that LSD can provoke long-lasting psychotic conditions.^[3,35] This was possibly responsible for the declining interest in using LSD to induce model psychoses.^[36] With psilocybin, a similar characteristic has been established over the years.^[37] In a study on healthy volunteers, it was reported for the first time that psilocybin-induced psychosis was due to 5HT2A receptor activation.^[37] Unfortunately, the present study did not include enough treatment data to conclude if overactivity of the 5HT2A receptor system was counteracted by rational pharmacotherapy, thereby possibly diminishing long-lasting unwanted effects of LSD-treatment.

4.3. LSD dose-index

In a subgroup of 81 neurotic patients, the acute outcomes of psychedelic treatment have been presented.^[5] A significantly higher LSD dose-index was found in the group of patients who with an acutely deteriorated condition (70, range 10–252) compared to the patients who improved (38, range 8–252). In the present study, the LSD dose-index was lower in the group of patients presented in Table 2. This finding is in line with the fact that a substantial number of the patients in Table 2 improved during acute LSD treatment. The finding also suggests that a lower LSD dose-index "predicts" a positive outcome, rather than a negative outcome, of LSD treatment. However, as nearly all the recorded patients in Table 2 reported severe long-term LSD-induced flashbacks at follow-up, a median LSD dose-index of 28 is still far beyond the cutoff point for neurotoxic development.

4.4. Psychedelic treatment: The state of the art. suggested benefits. connectedness

Several open-label studies on treatment-resistant depression and two controlled trials for cancer patients with anxiety and depression have suggested that single-dose treatment with psilocybin has “profound and enduring mental health benefits.”^[11 p. 1163,38,39] Further, LSD-treatment was advanced as being safe and effective when assisting psychotherapy for anxiety associated with life-threatening diseases.^[40] In order to understand this phenomenon, the concept of connectedness was introduced as a key to understanding how psychedelics work in clinical psychiatry, as well as in healthy controls.^[12,13] To quote a previous study, “we have proposed that brain serotonin 2A receptor signaling mediates a state of rapid plasticity that is conducive to major change . . . Such a function may be related to humans’ unique capacity for adaptability.”^[12 p. 549] However, as the authors stated, it is still necessary” to develop an operational definition of connectedness that incorporates not just connectedness in the subjective sense but also its biological basis and various behavioural manifestations.”^[12 p. 549] The present study and the Danish case study^[20] did not find any evidence for the occurrence of connectedness in the sense that it has been introduced in modern psychedelic research, in either subjective or objective descriptions of personality changes after LSD treatment.

4.5. Historical psychedelic treatment: Ignorance of unwanted effects

The authors of the 1964 paper on the outcomes of the first 129 patients treated with LSD at Frederiksberg Hospital were astonishingly ignorant of the side-effects of LSD-treatment, although they noted a homicide, 2 suicides, and 4 suicide attempts.^[7] They focused on clinical outcome and found that 59 out of 129 (45%) patients improved in accordance with almost the same short-term outcomes in a subgroup of Frederiksberg patients, as presented in Table 1 of the present paper. Concerning the homicide, it was even mentioned in the case report - which was kept in the Danish State Archives - that, after the second and third LSD treatments, the patient had homicidal impulses and needed belt fixation. The patient received a total of five LSD treatments with a dose of 50 µg, before stabbing the victim to death after the final treatment. In connection with LSD treatment, which was provided for depression, the patient had a revival of traumatic episodes from the past. However, immediately after the treatment, the patient was observed as being more honest and less inhibited, and thus was understood as having an improved condition. Today, such a change following an intervention would also be explained as a positive outcome that is, an antidepressant effect, as the patient was suffering from depression.

Concerning the suicides and the suicide attempts they could as well be attributed to factors other than the LSD administration. They could consequently be due to the mental condition, i.e., depressive disorder, which was the indication of the psychiatric treatment.^[41,42]

In Norway, for the treatment program involving 379 inpatients at Modum Bad, very few adverse effects were reported.^[43] However, a recent review revealed that the psychedelic treatment at Modum Bad did not always conform to guidelines for good practice, and there have been complaints of lasting psychological harm from the LSD treatments.^[44] Thus, a trend seems to exist in

early Scandinavian psychedelic studies: initial and partly uncritical enthusiasm that cannot be supported by future critical analyses.

4.6. Limitations

The present study was conducted retrospectively, as it relied on historical data that were never collected with the intent to elucidate if LSD treatment might induce changes in adult personality. Moreover, such a concept never appeared in the early Danish publications on psychedelic treatment. These publications simply addressed whether the treatment had curative potential.

Another serious confounder is the possible economic incentive for patients (LSD case material of 151 patients) to apply for financial compensation due to LSD-inflicted harm many years after the treatment took place. Thus, one might wonder why the remaining 250 patients did not also apply for compensation, as the LSD Damages Law included a reversed burden of proof. Unfortunately, case records of those patients have not been preserved, and we are currently unable to answer this question.

Along the same lines is the possible doubtful reliability of the data reported to the LSD tribunal. A short medical certificate was required and, for 111 of the 151 patients (74%), certificates from 20 different psychiatric specialists were obtained. In the mid-1980s, the financial compensation for LSD-inflicted harm ranged from 50,000 to 255,000 Danish krone, with some patients receiving up to 510,000 Danish krone based on the level of harm stipulated by the LSD tribunal. Patients who underwent psychosurgery or became severely psychotic were awarded the highest compensation amounts.^[4]

Much of the modern research on psychedelic therapy has been conducted with single, low to middle doses of psilocybin, in healthy volunteers and in selected patient populations in the borderlands of psychiatry. The LSD case materials reviewed in this study comprised a severely mental ill population, treated many times with high doses of LSD, and often as the last treatment of choice. Therefore, it may be difficult to make comparisons between this historical analysis and treatment experiences in the present day.

5. Conclusions

The overall findings from the present study indicated no observations of connectedness in a population of Danish patients who were treated with LSD from 1960 to 1974. Although descriptions of personality changes were recorded for a substantial number of patients, only in 2 to 4 cases were these changes long-lasting or permanent. The remaining described changes in adult personality may undoubtedly be considered as unwanted effects which persisted for weeks or months following acute treatment. Thus, they should be classified as side-effects in contrast to the symptomatic effects on clinical disorders, like depression, anxiety, or obsessions and compulsions, mediated by stimulating effects on brain receptors. The present study also included an analysis of a subgroup from the Danish patients who received LSD treatment before 1964.^[7] In this analysis, a similar percentage of patients with various psychiatric diagnoses were found to have improved following LSD treatment as in the 1964 analysis. However, in the 1964 study, little attention was given to side effects, such as those leading to one homicide, two completed suicides, and four suicide attempts: “The complications have

been few only and it seems absurd to have them tabulated.”^{17 p. 375} Future research should respect the potential toxicity of LSD, as well as other psychedelics, and possible unwanted effects should be systematically monitored. In psychiatric patient populations, psychedelics cannot be considered as drugs of choice, unless sufficient safety measures can be ensured.

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References

- Nutt D. Psilocybin for anxiety and depression in cancer care? Lessons from the past and prospects for the future. *J Psychopharmacol* 2016;30:1163–4.
- Grinker RR. Lysergic acid diethylamide. *Arch Gen Psychiatry* 1963;8:425.
- Rinkel M. Psychedelic drugs. *Am J Psychiatry* 1966;122:1415–6.
- Larsen JK. Neurotoxicity and LSD treatment: a follow-up study of 151 patients in Denmark. *Hist Psychiatry* 2016;27:172–89.
- Larsen JK. LSD treatment in Scandinavia: emphasizing indications and short-term treatment outcomes of 151 patients in Denmark. *Nord J Psychiatry* 2017;71:489–95.
- Larsen JK. LSD-behandling i dansk psykiatri. *Bibl Læger* 2013;205:224–65. (In Danish).
- Geert-Jørgensen E, Hertz M, Knudsen K, Kristensen KK. LSD-treatment. Experience gained within a three-year-period. *Acta Psychiatr Scand* 1964;40:373–82.
- Passie T, Halpern JH, Stichenroth DO, Emrich HM, Hintzen A. The pharmacology of lysergic acid diethylamide: a review. *CNS Neurosci Ther* 2008;14:295–314.
- Baumeister D, Barnes G, Giaroli G, Tracy D. Classical hallucinogens as antidepressants? A review of pharmacodynamics and putative clinical roles. *Ther Adv Psychopharmacol* 2014;4:156–69.
- Bech P, Allerup P, Reisby N, Gram LF. Assessment of symptom change from improvement curves on the Hamilton depression scale in trials with antidepressants. *Psychopharmacology* 1984;84:276–81.
- Pineyro G, Blier P. Autoregulation of serotonin neurons: role in antidepressant drug action. *Pharmacol Rev* 1999;51:533–91.
- Carhart-Harris RL, Erritzoe D, Haijen E, Kaelen M, Watts R. Psychedelics and connectedness. *Psychopharmacology* 2018;235:547–50.
- Watts R, Day C, Krzanowski J, Nutt D, Carhart-Harris R. Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. *J Humanist Psychol* 2017;57:520–64.
- McGlothlin WH, Cohen S, McGlothlin MS. Long lasting effects of LSD on normals. *Arch Gen Psychiatry* 1967;17:521–32.
- McGlothlin WH, Arnold DO. LSD revisited: a ten-year follow-up of medical LSD use. *Arch Gen Psychiatry* 1971;24:35–49.
- Strassman RJ. Adverse reactions to psychedelic drugs. *J Nerv Ment Dis* 1984;172:577–95.
- Abraham KD, Aldridge AM. Adverse consequences of lysergic acid diethylamide. *Addiction* 1993;88:1327–34.
- MacLean K, Johnson MW, Griffiths RR. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *J Psychopharmacol* 2011;25:1453–61.
- Larsen JK. LSD treatment in Scandinavia: the early enthusiasm and the resurgent interest. *Clin Pharmacol Toxicol Rev* 2018;1:13–8.
- Brandrup E, Vanggaard T. LSD treatment in a severe case of compulsive neurosis. *Acta Psychiatr Scand* 1977;55:127–41.
- Erritzoe D, Richards WA. Lessons to be learned from early psychedelic therapy in Denmark. *Nord J Psychiatry* 2017;71:487–8.
- LSD Damages Law. Law on compensation for damages by LSD-treatment. Christiansborg Slot: Law no. 219; April 23th; 1986.
- Hertz M. Observationer og indtryk fra et års arbejde med LSD. *Nord Psyk Tidsskr* 1962;16:103–8. (In Danish).
- Hertz M, Abramson HA. The mechanism of the LSD treatment as viewed from the aspect of learning processes. The use of LSD in psychotherapy and alcoholism. 1968;The Bobbs-Merrill Company, Inc, 333–40.
- Akers J, Riley R. The psychedelic renaissance: ethnopharmacology, neuroscience and clinical efficacy. *Australasian anaesthesia 2019; Australian and New Zealand College of Anaesthetists*, 203–17.
- World Health Organisation (WHO) Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, 6th edn (ICD-6). Geneva: WHO; 1949.
- World Health Organisation (WHO) Manual of the International Classification of Diseases (ICD-8). Geneva: WHO; 1965.
- 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. (In Danish).
- Erritzoe D, Nutt DJ, Carhart-Harris R. Concerns regarding conclusions made about LSD-treatments. *Hist Psychiatry* 2017;28:257–60.
- Leuner H, Holfield H. Ergebnisse und Probleme der Psychotherapie mit Hilfe von LSD-25 und verwandten Substanzen. *Psychiatr Neurol* 1962;143:379–91. (In German).
- Sandison RA, Spencer AM, Whitelaw JDA. The therapeutic value of lysergic acid diethylamide in mental illness. *J Ment Sci* 1954;100:491–507.
- Strömgen E. *Psykiatri*. 8th ed Copenhagen: Munksgaard; 1964. (In Danish).
- Kringlen E. *Psykiatri*. 7th ed Oslo: Gyldendal Norsk Forlag; 2001. (In Norwegian).
- Vanggaard T. Indications and counter-indications for LSD treatment. *Acta Psychiatr Scand* 1964;40:427–37.
- Fisher DD, Ungerleider JT. The chronic side effects from LSD. The problems and prospects of LSD. Springfield, Illinois: Charles C. Thomas Publisher; 1968;69-79.
- Hofmann A. LSD, My problem child. New York: McGraw-Hill Book Company; 1980.
- Vollenweider FX, Vollenweider-Scherpenhuyzen MFI, Bäbler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via serotonin-2 agonist reaction. *Neuroreport* 1998;9:3897–902.
- Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open label feasibility study. *Lancet Psychiatry* 2016;3:619–27.
- Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decrease in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol* 2016;30:1181–7.
- Gasser P, Holstein D, Michel Y, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *J Nerv Ment Dis* 2014;202:513–20.
- Bolton JM, Pagura J, Enns MW, Grant B, Sareen J. A population-based longitudinal study of risk factors for suicide attempts in major depressive disorder. *J Psychiatr Res* 2010;44:817–26.
- Yeh HH, Westphal J, Hu Y, et al. Diagnosed mental health conditions and risk of suicide mortality. *Psychiatr Serv* 2019;70:750–7.
- Madsen JD, Øyslebø T, Hoffart A. A follow-up study of psycholytic therapy with the aid of LSD. *Nord J Psychiatry* 1996;50:487–94.
- Johnstad PG. A dangerous method? Psychedelic therapy at Modum Bad, Norway. *Hist Psychiatry* 2020;31:217–26.