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Psilocybin in the treatment of anorexia nervosa: The English transition of a French 1959 case study

La psilocybine dans le traitement de l'anorexie mentale : la traduction en anglais d'une étude de cas française de 1959

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ABSTRACT

Psilocybin is a psychotropic molecule that is a partial agonist of serotonin 2A receptors and is the main psychoactive compound in hallucinogenic mushrooms. After the observation in 1953 in Mexico of ritual practices involving ingestion of such mushrooms, psilocybin was chemically characterized and synthesized in 1958 thanks to the collaboration between the *Muséum national d'Histoire naturelle* in France and the Sandoz pharmaceutical laboratories in Switzerland. The interest of this substance in psychiatric therapy was then evaluated for the first time at the Sainte-Anne Hospital in Paris, by the team of Professor Jean Delay. Among the patients who received this substance was a 35-year-old woman who was hospitalized for compulsive manifestations emblematic of anorexia nervosa and who experienced an immediate and lasting improvement. The original 1959 article (published in the *Annales de la Société Médico-Psychologique)* gives details of the patient's family background, biography and clinical examination. It then outlines the observations after two injections of psilocybin four days apart, in particular the autobiographical verbal statements that allowed the patient to understand the psychogenesis of her illness. After a long hiatus, psilocybin is once again the subject of medical research, with clinical trials now underway assessing psilocybin in the treatment of anorexia nervosa (NCT04505189; NCT04052568; NCT04661514) and this 1959 case study, is the first known demonstration of the safety and efficacy of psilocybin treatment of anorexia nervosa. This case study thus provides an interesting insight into possible therapeutic mechanisms and is of great interest to the field moving forward.

Mots clés :
Anorexie mentale
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Hallucinogène
Thérapeutique médicamenteuse

RÉSUMÉ

La psilocybine est une molécule psychotrope agoniste partielle des récepteurs sérotoninergiques 2A qui constitue le principal composé psychoactif des champignons hallucinogènes. Après l'observation, en 1953 au Mexique, de pratiques rituelles d'ingestion de tels champignons, la psilocybine a pu être caractérisée chimiquement et synthétisée en 1958 grâce à la collaboration entre le Muséum national d'Histoire naturelle en France et les laboratoires pharmaceutiques Sandoz en Suisse. L'intérêt de cette substance en thérapeutique psychiatrique a ensuite été évalué pour la première fois à l'hôpital Sainte-Anne à Paris, par l'équipe du professeur Jean Delay. Parmi les patients ayant reçu cette substance, une femme de 35 ans, internée pour des manifestations compulsives liées à l'alimentation et anorexique,

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connut une amélioration immédiate et durable. Alors que la psilocybine fait aujourd'hui de nouveau l'objet de recherches médicales, ce cas, publié en 1959 dans les *Annales Médico-Psychologiques*, constitue la première étude connue sur l'efficacité du traitement de l'anorexie mentale par ce composé. L'article de 1959 donne des détails sur le milieu familial, la biographie et sur l'examen clinique de la patiente. Il expose ensuite les observations après deux épreuves à la psilocybine, en particulier les énonciations verbales autobiographiques permettant à la patiente de comprendre la psychogenèse de sa maladie. Cette étude de cas apporte ainsi un regard intéressant sur les possibles mécanismes thérapeutiques, alors que trois essais pour évaluer l'intérêt de la psilocybine dans le traitement de l'anorexie mentale sont actuellement en cours au Royaume-Uni et aux États-Unis (NCT04505189; NCT04052568; NCT04661514) et que d'autres sont en préparation.

The purpose of this paper is to present the English translation of a French article published in 1959 in the *Annales Médico-Psychologiques* on the case of a woman with anorexia nervosa (AN) treated with psilocybin at the Sainte-Anne hospital in Paris, France: « Effets de la psilocybine sur une névrose compulsive » [11] (''Therapeutic effect of psilocybin on a compulsive neurosis''). It should be noted that the title of the article contains a misprint in the original publication: it should read ''*compulsive*'' instead of ''*convulsive*'', as confirmed by the bibliographic reference in Anne-Marie Quétin's thesis ''*La psilocybine en psychiatrie clinique et expérimentale*'' published in 1960 [21].

AN is clinically defined as severe nutritional restriction, an intense fear of gaining weight, and a disturbance of one's bodily self-perception [1]. It is the most fatal of all psychiatric conditions with mortality rates between 5 and 11 times higher than the general population, ''with one in five deaths being by suicide'' and one in five of those who die with AN by suicide [3]. Fewer than half those diagnosed reach remission after specialist treatment and approximately 60% still meet diagnostic criteria 20 years after diagnosis [5]. There is a desperate need for new treatment avenues to be explored and it has been argued that greater efficacy may come from treatments that target the deeper disturbance of identity, connection to the body, and self-worth that characterise the condition [9,10,24].

Psilocybin is a psychotropic molecule produced by different species of mushrooms that have been used for several centuries by Amerindian peoples in the Mesoamerican cultural area [12,15]. Today, psilocybin and so-called ''magic mushrooms'' are listed in Schedule I of the 1971 Convention on Psychotropic Substances. It was through a collaboration between the *Museum national d'Histoire naturelle* (MNHN) in France and the pharmaceutical laboratory Sandoz in Switzerland that this indolic molecule with a phosphoric acid radical was discovered in 1958. Professor Roger Heim (1900–1979), mycologist and director of the MNHN, had been invited by the amateur ethnologists Robert Gordon Wasson (1898–1986) and Valentina Pavlovna Wasson (1901–1958) to identify samples of divinatory mushrooms collected in Mexico from 1953 onwards. In Paris, Professor Heim quickly succeeded in identifying, naming, and cultivating the collected species. It was the development of a semi-industrial method of cultivating *Psilocybe mexicana* Heim by Roger Heim and Roger Cailleux (1929–1999) in France that paved the way for Albert Hofmann and his colleagues to identify the active component in 1958 at Sandoz laboratories, Switzerland [17].

And so, after the characterization and development of psilocybin, Roger Heim had tablets and injectable solutions of this new substance transferred from Sandoz laboratories to the department of psychiatrist Professor Jean Delay (1907–1987) at the Sainte-Anne mental hospital in Paris. There, from July 1958 onwards, Delay and his colleagues began to explore the physiological and psychic action of psilocybin and to evaluate its therapeutic possibilities by testing the substance on healthy volunteers and psychiatric patients [9,10]. It was in this context that Miss Henriette B. . ., hospitalized for compulsive neurosis related to AN, received two injections of psilocybin. This case was presented to the *Société Médico-Psychologique* at the meeting of 3 July 1959 and published the same year in the bulletin of this learned society [11]. Here, we present a translation of this case study into English, in order to make it better known to the research community interested in the therapeutic use of serotonergic psychedelic substances.

This case study presents one such example of the promising therapeutic results from research conducted between the 1950s and 1970s [14] that have provoked the recent scientific resurgence of psychedelics in the treatment of psychiatric conditions [20]. Psilocybin is one example of this group of classic serotonergic psychedelics which also includes lysergic acid diethylamide (LSD), and dimethyltryptamine (DMT), and which all exert their subjective effects through the partial agonism of the Seretonin type 2a receptor (5-HT2A) [19].

Psilocybin is the most commonly utilized psychedelic compound in therapy, which typically consists of one to three high doses of psilocybin (25–30 mg) delivered in a supportive context. Each session is enveloped by psychotherapy before (i.e., psychological preparation) and after (i.e., psychological integration) the dosing, which is considered central to achieving therapeutic success [8]. A recent systematic review across 10 trials (188 patients) demonstrated the feasibility and possible efficacy of psychedelic assisted therapy across conditions such as depression, anxiety, obsessive compulsive disorder, and substance use disorder [2].

Whilst it would be incorrect to say that psilocybin is a panacea for all psychiatric conditions, several theories spanning neural, computational and psychological levels have emerged as to how psychedelics may work in a transdiagnostic manner. The Relaxed Beliefs Under pSychedelics (REBUS) model specifies how the precision of prior beliefs are relaxed under psychedelics, allowing for the formation of new thoughts and ideas after the experience. Not only does this provide the basis for alteration in the self-perception of the bodily self [16], but it allows individuals to form new insights into their psyche and previous trauma [7]. The 'pivotal mental states' hypothesis extends this model and posits that psychedelics induce a hyper-plastic state that promotes rapid and deep learning which, in the right context, can mediate psychological transformation [6]. It is this relaxation of prior beliefs (REBUS model) and hyper-plastic state (pivotal mental states) that may facilitate changes in one's concept of Self and Body.

On the basis of this growing body of evidence, it seems a natural next-step to explore psychedelic assisted therapy as a novel treatment avenue for AN [13]. Three such studies are now underway in the UK and North America (NCT04052568, NCT04505189, NCT04661514), with additional studies in the pipeline [4]. Grounding for clinical trials with psilocybin in the

treatment of AN is also provided by naturalistic studies, since such studies have demonstrated increases in self-acceptance, self-love and wellbeing, and decreases in depression symptomology following a self-initiated psychedelic experience in those suffering from an eating disorder [18,22,24]. The case study, presented by Jean Delay and his collaborators at the early stages of experimentation with psilocybin, also demonstrates the therapeutic potential of this compound which was ''indisputable'' according to the authors. Through the experience, the patient gained insight into the psychogenesis of her eating disorder, showed increased intellectual and affective awareness of her problems, and had lasting improvement in her mood [11]. It is also interesting to note the author's recognition of acute emotional breakthrough in facilitating this patient's subsequent improvements; a factor now recognised as an important mediator of post-acute change [23]. While the patient's improvements were not maintained 1 year later [21], there is no report of post-acute psychotherapeutic integration, which is an important component of modern implementations of psilocybin-assisted therapy and is deemed critical for facilitating long-term benefit. In summary, this case study not only represents the first known documentation of the safety and possible efficacy of treating AN with psilocybin, but also provides intriguing insight into possible therapeutic mechanisms.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Therapeutic effect of psilocybin on a compulsive neurosis

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Translated by Rayyan Zafar and Vincent Verroust from: Delay J, Pichot P, Lempérière T, Quétin, A-M. Effet de la psilocybine sur une névrose convulsive. Annales Médico-psychologiques, revue psychiatrique. 1959;(117):509–15.

OBSERVATION. – Miss Henriette B. . ., 35 year old, works in a tax office and hospitalised in service on the 23rd March 1959 for compulsive mannerisms concerning food. The sight of food triggers a need in her to eat everything immediately which leads to intense remorse.

This patient, who described herself as bulimic, presented nevertheless with a very precarious state of health: her weight is barely 40 kg for a height of 1 m 69 cm. In addition, this presentation comes with depressive-like symptoms including asthenia, insomnia, dark thoughts and lack of confidence.

The current state of this patient cannot be fully understood without a thorough investigation of her family environment and history.

FAMILY ENVIRONMENT: Henriette B. . . was born to a small and functional family where there was no history of previous psychopathy or psychosis. She has always suffered from a stifling atmosphere at her home. Life has been calm and regulated, without originality, dominated by the rigorous morality of her parents. Permanent financial difficulties, low levels of parental intelligence, badly supported this spirited child with a lively intelligence.

The mother is the dominant figure in the family. Hyperactive and a perfectionist, she holds the authority. She is only concerned about the material well-being of her family. The father, an accountant, ''fussy'', is passive to his wife and devotes his limited spare time to charity work. A sister who is 2 years younger than the patient, married to a provincial tax collector, is completely opposite to her. The mother always compared her two daughters to devalue the older one. A brother, 7 years younger, developed Pott's disease in his childhood. The mother, of which he was her favourite, always refused to hospitalize him and now he is bedridden and has been for 10 years. He still lives with them and he is taciturn and bitter.

HER BIOGRAPHY: She was born on the 7th June 1924, she was breastfed for a year. Weaning was easy, but her appetite was temperamental following this. Around 5-6 years, there was one indisputable episode of anorexia. The mother, who told us about it, could not give us a particular reason why. During this time, the very worried child, presented with nightmares and fear of the dark. Her schooling was marked by a great psychomotor inability, which led the mother to continue to compare her 2 daughters.

Despite her very changeable mood and indiscipline, she passed her school exams in 1941. She wanted to be a schoolteacher or woman of letters (she has written a lot of poems) which her mother used to make fun of her for.

Due to economic difficulties in the family, the patient became discouraged and interrupted her studies. A little while after, she entered the financial administration and still has a low-level job there. Her repeated failures in various competitive exams can only be explained by an unconscious refusal on her part. She has adapted very well to her work environment where they consider her quite eccentric.

DISORDER HISTORY: The start of her problems was in 1943. Multiple factors began here: problems with finances due to the illness of her brother, suppression of the professional aspirations of the patient. Food issues were at this time a major problem for her family, who refused everything that comes from the 'black market', as a matter of principle.

Henriette was depressed, sad, often cried, she felt useless and good for nothing. She decided to voluntarily stop eating. She lost 20 kg in 1 year. Her periods stopped. But this voluntary restriction did not suppress her appetite. She began to steal her family's bread ration of which she immediately regretted. She was hospitalized twice under the care of Prof. Heuyer where she was force fed (1943-1944). Her weight increased but her periods did not come back. She could restart her job and live a semi-normal life up until 1952, where she was being treated again, this time for compulsive eating. For the same reason, she was hospitalized again in 1956 for a few weeks.

CLINICAL STUDY: On entry, the patient described to us the troubles that bother her, and she said above all it is about cravings. Whenever food is in front of her, she feels obliged to eat all of it straight away. When she is with her parents or at her sisters, this imperious hunger pushes her to steal food.

These are truly compulsive acts that are accompanied by extreme anguish, but there is no fight against this need that she considers irresistible. She did not establish any rite of defence. The act is not followed by any relief, it leads to intense remorse. The fluctuations in her mood play an important role. In times of happiness, she is able to accommodate her troubles. In depressive periods, she is submerged by guilt, her cravings are exaggerated by anxiety, she is locked in a vicious circle. Each of her hospitalisations have been initiated by a depressive period.

Her way of life hit us as having extreme regularity. Everything is planned to the minute. Every day she feels the need to exercise intensely (for example 20 km of walking). She only allows herself

to be distracted by things she considers to be cultured. Theatre, cinema, books, all carefully chosen.

She extremely limits her spending on clothes and when she buys a new dress, she immediately donates an old one. She is besides fixed on a number of clothes that she cannot exceed. The singularly rigid nature of this existence is not unnoticed by our patient, who tries to rationalise her existence: 'she cannot afford herself luxuries, if all over the world there are people living without basic essentials'.

She is aware of the self-centeredness of her life. She ritually visits her parents once a week. Despite her love for children, she cannot stand her nephews, who tire her out. Her emotional and sexual life is null. In 1946, following her sister's marriage, she thought she would get engaged to one of her colleagues, but they broke up for a futile reason. It is through religion that she tries to fill her emotional void. She speaks of her 'spiritual cravings' as much as she speaks of her food cravings. Daily communion is her 'spiritual nourishment' and for her a true need. But religion also offers her more, the dream of a future where she can finally be liberated from her 'body' that she never could accept.

PHYSICAL EXAMINATION: The patient is very skinny, 40 kg for 1.69 m. The skin is dried, hair is brittle and body hair poorly developed. There is significant acrocyanosis. She has had amenorrhea since 1952.

COMPLEMENTARY EXAMINATIONS: Urea = 0.58, Blood proteins 57 Alb.Glob. 29/28 104. Blood sugar 0.70. Numbers and formulation of blood normal. Normal sella turcica x-ray. Pap smear shows hypo-oestrogen manifestation.

Electroencephalogram: Discretely altered trace, irritative aspects, presence of elements Theta in the left posterior hemisphere (Dr Verdeux)

Psychometric Examination:

1) Tests used: Intelligence scales Wechsler-Bellevue 1, Original calibration, Binois-Pichot vocabulary test, visual retention test of Benton, MMPI, Rorschach test, T.A.T
2) Results The subject has a higher than average level of intelligence. Wechsler-Bellevue scale: I.Q Verbal = 119, IQ performance = 130 IQ total = 126. Benoit-Pichot vocabulary test IQ = 119

The culmination of received tests do not indicate a pathological character or a significant and precise diagnosis. We have only found some discrete neurotic traits which go together with anxiety and with some weakly structured mechanisms of obsessional and especially compulsional type. But the most dominant aspect is a certain emotional immaturity in relation to problems with psychosexual adaptation, leading her to take refuge in idealisation and intellectualisation. There is also aggressiveness towards her mother, for which she feels guilty, and a secondary feeling of exclusion and emotional frustration.

OBSERVATION IN THE DEPARTMENT: At her entry to the clinic, the patient was isolated and subjected to treatment with Largactil (Chlorpromazine). There was almost no result, 3 weeks later she was still as depressed as she was before, and her weight had not changed. It was at this point that we gave her the first injection of psilocybin.

1st Injection of Psilocybin: It was done on the 20th April 1959, the patient was still receiving 100 mg largactil daily. At first it only gave ordinary neuro-vegetative and short-lived reactions. The psychological reactions only showed a bit later when she was in her room by herself. We learnt the next day, by the report she made verbally, and through the writings of poems that she wrote during the fecund part of her experience. She had poly-sensory hallucinations, physical metamorphosis, changes to her mood that are described with abundance and ease. Certainly, these manifestations are commonplace during a psilocybin injection, but they are usually poorly formulated and incommunicable.

In our patient, the expansiveness of her mood, together with a gift for poetic expression, permitted a relatively easy to understand verbal portrayal of the 'delirious experience' of which a long habit of introspection has allowed her to examine the smallest details. Euphoria dominates it, the titles of her numerous poems testify this: ''Hallelujah, Plenitude, Spring, Eden, Euphoria''. Multiple hallucinations, agreeably perceived, contributed to creating a vision of paradise, whose description seems somewhat naïve to us 'Angels play the flute, rum perfumes, pure and clear blue atmosphere, amazing harmony'. Time does not exist anymore: 'I am suddenly young, for eternity'. What enchanted her the most was her deliverance of carnal bonds, her transparency, her purity and her lightness. 'I am flying on a ray of the sunlight, I am giddy, I no longer feel the weight of my liberated flesh, my body, my old constraint, feels lifted . . . I don't have a body anymore; I am only a soul and I am real'.

2nd Injection of Psilocybin: The second injection of psilocybin was given 4 days later while treatment with Largactil had been suspended. She presented with extremely intense psychological reactions: semi-confusional state with physical discomfort for half an hour, during which dreamlike scenes with mystical themes took place: Agony of Christ, resurrection and visions of heaven.

She slowly left this confused state to enter a phase of emotional reliving, which lasted close to 2 hours. The intensity of feelings expressed contrasted with the normal presentation of the patient, really reserved normally. She tried to control her aggressiveness by challenging every critique with a counter proposal.

Here are the principal themes expressed:

Emotional frustration: 'it's always the same question, I always have the impression that I am not liked (theme comes up a lot. . .), I suffer from a lack of affection. Especially from my professors. I was criticised for not being very open'

A great deal of aggression against her mother: 'My mother, I don't judge her, she did not have a sufficient education. She had a very unfortunate upbringing. She wanted us to have possession, solely possessions, she never understood that I may have wanted something more than that, she remained basic. I am more intellectual, I am more sensible. As long as we have the material, that's sufficient for her. That did not suffice me. She always says to me 'You never lacked anything'. The opening of the heart and soul is what she did not give to me. She pulled my hair. Oh, what did I say, Oh, that's awful, I should not accuse her, mummy is a poor woman. I am accusing her, even though I love her. Basically, it's my mum that's responsible. I know it's not her fault, but she is responsible. Yesterday my poor mum came to visit me, she bought me food. I myself am aware of the origin of my illness. Poor mum. She is responsible. I know it, but I have a sense of guilt. She used to tell me that I was making her bleed. . . Mummy, I accuse her and at the same time excuse her.

Fixation on father: 'My dad is very good, comprehensive, very in the shadows. He used to get angry about my homework, although he also had patience at the same time; it struck me more than mum. When he was punishing me, it was judicious. Dad is more intellectual than mum. How did they get on so well? Mummy is basic'.

In the course of her childhood, 2 women played a very important role in her emotional life.

A neighbour, Mrs F. . . whom she called mummy, and 'who loved me a lot, unlike my mother'. The first episode of anorexia was at 6 years old and coincided with moving away from this neighbour, a person she would continue to visit every week until she died.

A schoolteacher, Ms D. . ., that she had at the age of 10. 'She incarnated for me the ideal mother. Her face comes back to me, very much in my mind. To please her (I remember this feeling very well), I used to finish my work quickly. She really portrayed to me the image of the teacher that I would have wanted to be.'

Feelings of guilt: 'My case, it's almost a religious case, I have always had the feeling of guilt, it's strange'. It was only me who was fed by mum, that attached me more to her. That may have given me more guilt towards her. I was the only one to be fed like this'.

Finally, when she talks about the trauma of her first period, she tells us 'I had a moment of anguish. I must have made a mistake. I have always had this feeling of guilt'.

Feelings of inferiority: 'I still have the impression of being inferior to them (her family). I feel like I have stolen something from them intellectually. I could have done better.'

Anorexia: She speaks about her problems with food from childhood and states the start of her troubles being in 1943, during the war. She suggests that it was not a loss of appetite, but a voluntary restriction so painful that she was sometimes obliged to steal bread in secret.

Food compulsions: 'I realize that, in my cravings, I have to fulfil a nervous need. It was just me that was fed by mum and that attached me to her more'

Sexual difficulties: This is the first time she has spoken about it without reluctance. 'As I was very withdrawn, I was not told about the first day of my period. I found it all a bit disgusting. I didn't dare ask for anything. Sex, I would have to love a lot to overcome this act. Luckily, I have Bruno' (her teddy bear).

Depressive episodes: Throughout her childhood, she believed she was rejected by her mother, she had the desire to leave or to kill herself.*

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Evolution: The recovery was immediate. The next day, the patient was euphoric. Her weight increased rapidly. At her discharge, one month later, she had put on 7 kg. She regularly spoke with us about her expérience, which she considers very beneficial.

CONCLUSION

In this patient, psilocybin has had an indisputable therapeutic action. The comparison between the results of the two injections is very instructive.

The first, given under Largactil, gave no rise to emotional breakthrough or affective revival. It only allowed the patient to express in a euphoric way her fundamental aspiration to be released from her body.

The second, given without Largactil, gave rise to a flux of memories. Without any control and extreme violence, she exposed to us what she considers to be the psychogenesis of her illness and also her gripes against her mother. Memories of her childhood that she forgot came back very emotionally, in particular the separation from someone she considered her second mother, Madame F. . . The first episode of anorexia at 6 years was thus explained.

It was this second injection of psilocybin that led to the definitive recovery of the patient *[authors' note: Anne-Marie Quetin's thesis reveals that a year later she found herself depressed again]*. Intellectual and affective awareness of her problems, as well as durable transformation of her mood seem to us to be the determinants of her change.

DISCUSSION

Mr Dublineau – The association of impulsive factors and mystical elements of the type reported here evoke a reaction of dysrhythmia of a para-convulsive type. The presence of slow waves on the EEG examination in this patient, could, in spite of the rather banal character of them, constitute a supporting argument of a hypothesis of this kind.

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